UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: December 26, 2018

SUBJECT: **Naphthalene:** Human Health Risk Assessment in Support of Registration Review

PC Code: 055801
Decision No.: 530531
Petition No.: N/A
Risk Assessment Type: Single Chemical/Aggregate
TXR No.: N/A
MRID No.: N/A

DP Barcode: D440842
Registration Nos.: See table 3.3
Regulatory Action: Registration Review
Case No.: 0022
CAS No.: 91-20-3
40 CFR: N/A

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This assessment has been conducted to address the requirement for a Draft Risk Assessment (DRA) to support Registration Review. As part of Registration Review, the Pesticide Re-Evaluation Division (PRD) of the Office of Pesticide Programs (OPP) has requested that the Health Effects Division (HED) evaluate the available hazard and exposure data and conduct dietary, occupational/residential, and aggregate assessments to estimate the risk to human health that may result from the currently registered uses of naphthalene.

1.0 Executive Summary

HED has conducted a human health DRA as part of Registration Review to evaluate all existing registrations of the pesticide active ingredient (ai) naphthalene. Naphthalene was previously assessed in the amended HED chapter of the Registration Eligibility Decision Document (RED) (D335946, D. Drew et. al., 02/28/2008). The current assessment reflects updates to points of departure (PODs) and uncertainty factors (UFs), as well as updates to HED's Residential standard operating procedures (SOPs). In addition, recently-submitted chemical-specific air concentration data and recently Human Equivalent Concentrations (HECs) were calculated and have been incorporated in the assessment. The current assessment considers dietary (drinking water), residential, occupational, and aggregate exposures.

Use Profile

Naphthalene is a crystalline solid that is manufactured into mothballs, flake, and granule products containing 99.85% to 99.95% naphthalene.

These products are registered for use indoors to repel moths from clothing stored in airtight containers or enclosed areas (e.g., closets) and to repel nuisance vertebrate pests (e.g., bats and tree squirrels) from indoor areas such as attics and wall voids. In addition, there are naphthalene granule products that are registered for use outdoors to repel animals such as snakes, rats, mice, squirrels, rabbits, deer, dogs, and cats from sites such as buildings, wood piles, trash cans, and ornamental gardens. One of the naphthalene products labeled for outdoor use is a repellent station containing granules; the other naphthalene products labeled for outdoor use are loose granule products with use directions that instruct that the granules should be applied as a narrow band around the target areas. No personal protective equipment (PPE) is required for any registered labels of naphthalene. The current assessment considers both indoor and outdoor uses of naphthalene.

To minimize the potential for children to be exposed to naphthalene through ingestion of loose mothballs, as of September 30, 2013, all naphthalene mothball products must have the mothballs packaged and sold in sachets. This was required per the 2008 Naphthalene Reregistration Eligibility Decision to mitigate risks associated with the incidental ingestion of mothballs. This mitigation applied only to mothball products; there are no specific packaging requirements for the naphthalene granule and flake products.

Exposure Profile

Based on the currently registered uses of naphthalene, short-term residential dermal and inhalation exposures may result from applying the naphthalene products. There is potential for short-, intermediate-, and long-term residential post-application inhalation exposures following indoor applications. Post-application inhalation exposures are not expected for the outdoor uses. While there may be potential for residential post-application dermal exposure, a residential post-application dermal assessment was not conducted since a dermal endpoint was not selected. Exposures resulting from non-occupational spray drift or off-field bystander volatilization are not expected based on the formulation of naphthalene and how it is applied.

There is the potential for episodic ingestion of naphthalene flakes or granules by children because the flakes may be applied indoors, sprinkled inside closets and storage containers, and the granules may be applied to indoor areas that could be accessible to children, such as attics. In addition, there is also an opportunity episodic ingestion of granules that are labeled for outdoor application around areas that are potential accessible to children, including the perimeter of houses, cabins, trailers, garages, barns, trash cans, flower beds, etc). The episodic ingestion scenario for naphthalene that is likely to produce the most exposure is episodic ingestion of moth flakes that are applied indoors. Incidental oral (hand to mouth) exposures are not expected since those scenarios describe a child contacting a surface with residue from a treatment, which is not expected based on how naphthalene is applied and the nature of the products.

Occupational handler exposures are expected; occupational handlers may be exposed to naphthalene during indoor and outdoor applications in residential settings. Occupational post-application exposures are not expected, as occupational handlers who apply mothball products in a residential setting would not be expected to remain in that residential setting for a time period sufficient to result in significant exposure.

Naphthalene is a non-food use pesticide. There are no U.S. tolerances and exposures are not expected through food based on the registered pesticidal uses. Exposures via drinking water are possible because residues of naphthalene could potentially reach drinking water through run-off from its registered use as an outdoor animal repellant. A drinking water-only dietary assessment was conducted.

Hazard Characterization and Dose Response Assessment

The toxicology database for naphthalene is complete. The Hazard and Science Policy Council (HASPOC) has recommended that a two-generation reproductive toxicity inhalation study in the rat be waived (TXR# 0057813, 11/01/2018). The database consists primarily of inhalation studies, since this is the main route of exposure. Naphthalene inhalation studies include both nose-only (4-week, 13-week, and subchronic 90-day neurotoxicity) and chamber (whole body exposure) studies (2 year) in rodents. These studies indicate that naphthalene is a nasal toxicant in rodents at low concentrations.

Subchronic oral toxicity of naphthalene is manifested as body weight changes, organ weight changes, and/or clinical signs of toxicity. In a 90-day dermal toxicity study in the rat, effects were noted only at the high dose of 1,000 mg/kg/day. No effects were noted at 300 mg/kg/day. A quantitative dermal risk assessment is not required because effects were only observed at the limit dose (1,000 mg/kg/day) in the route-specific study and dermal exposures are expected to be minimal. There is no quantitative or qualitative susceptibility in the developmental toxicity studies.

There was evidence of neurotoxicity (e.g., loss of olfactory neurons following inhalation exposure, and hunched posture and decreased motor activity following oral treatment); however, the neurotoxicity was either limited to portal of entry effects in the inhalation studies or attributed to the bolus gavage administration in the oral toxicity studies. The concern for loss of olfactory neurons is low since there are clear LOAELs/NOAELs and endpoints selected for risk assessment are protective of these effects. There were no effects on brain weights or brain neuro

histopathology in well-conducted NTP studies with naphthalene. There was no evidence of increased susceptibility (quantitative or qualitative) of rat or rabbit fetuses to *in utero* exposure to naphthalene. In the rat, the developmental no observed adverse effect levels (NOAELs) are higher than maternal NOAELs. In contrast to rodents, humans are susceptible to the hemolytic effects of naphthalene exposure.

The carcinogenic potential of naphthalene is currently undergoing review by the EPA's National Center for Environmental Assessment (NCEA; Integrated Risk Information System (IRIS)). Naphthalene has not been subjected to a full EPA/International Programme of Chemical Safety (IPCS) framework for the analysis of a cancer mode of action (MOA) and relevancy of animal MOA to human carcinogenicity. EPA's Health Effects Division has not performed a quantitative cancer risk assessment for naphthalene.

The POD for chronic dietary exposure is derived from the results (decreased body weight) of the subchronic oral toxicity study in the rat. For this scenario, a total uncertainty factor of 1000X (10X for interspecies extrapolation, 10X for intraspecies variation, and a 10X uncertainty for subchronic to chronic extrapolation) is appropriate. The acute dietary endpoint (general population) was selected from the acute neurotoxicity (ACN) oral study in rats based on hunched posture in females, head shaking in males and females, and reduced motor activity in males and females. For the acute dietary POD, the total uncertainty factor is 1000X (10X for inter-species extrapolation, 10X for intra-species variation, and a 10X uncertainty factor for lowest observed adverse effect level (LOAEL) to NOAEL extrapolation). The short-term inhalation POD was derived from a 4-week (nose-only) inhalation rat study based on nasal lesions, and the intermediate-term inhalation POD was based on the subchronic neurotoxicity (SCN) (nose-only) rat inhalation study based on nasal lesions. For both the short- and intermediate-term PODs, a total uncertainty factor of 30X (3X for interspecies extrapolation [the HEC accounts for the pharmacokinetics component of the interspecies extrapolation], 10X for intraspecies variation) was applied. The long-term inhalation endpoint was selected from a chronic toxicity and carcinogenicity inhalation study in the rat based on nasal lesions, with a total uncertainty factor of 300X (3X for interspecies extrapolation, 10X for intraspecies variation, and a 10X uncertainty factor for extrapolating a lowest observed adverse effect concentration (LOAEC) to no observed adverse effect concentration (NOAEC)).

Dietary Exposure Assessment

Naphthalene is a non-food use chemical because it is not applied to crops grown for food or feed. There are no agricultural uses or existing tolerances. However, a dietary assessment is conducted because residues of naphthalene could potentially reach drinking water through run-off from its registered use as an outdoor animal repellant. The acute and chronic dietary analyses are high-end screening level assessments of naphthalene exposure from drinking water. They are based on modeling results provided by the Environmental Fate and Effects Division (EFED) which estimate the concentration of naphthalene in water.

The acute dietary risk estimate for naphthalene was <1% of the acute reference dose (aRfD) at the 95th percentile for the general U.S. population. The most highly exposed population subgroup was all infants < 1 year old, which had an acute exposure of 1.8% of the aRfD at the 95th

percentile. The chronic dietary risk estimates for naphthalene were <1% of the chronic reference dose (cRfD) for the general U.S. population and all its population subgroups.

Residential Exposure and Risk Assessment

Inhalation risk estimates of concern were identified for residential handlers (margins of exposure (MOE) < level of concern (LOC); LOC = 30). MOEs ranged from 0.82 to 14 for the indoor application of moth flakes. The use of surrogate plunger duster data for dusts for the application of moth flakes is considered highly conservative as it is representative of powdery type dusts. Risks for moth flakes would likely be lower. No risks of concern were identified for residential handlers applying granules to outdoor environments; MOE = 49 (LOC = 30). MOEs for residential handlers applying granules indoors via hand dispersal ranged from 29 to 490 (LOC = 30). A summary of these residential handler inhalation exposure and risk estimates for naphthalene are presented in Table 6.1.1

All short-, intermediate-, and long-term residential post-application scenarios result in MOEs less than the LOC (short- and intermediate-term inhalation LOC=30; long-term inhalation LOC = 300) and are of concern. Short-term MOEs range from 22 to 23 for adults and 19 to 21 for children (1 to < 2 years old). Intermediate-term inhalation MOEs range from 6.3 to 6.8 for adults and 5.6 to 6.1 for children (1 to < 2 years old). Long-term MOEs range from 75 to 81 for adults and 67 to 72 for children (1 to < 2 years old).

In general, episodic ingestion represents the potential exposure and risk that would be caused by ingestion of pesticide pellets and granules that have been applied to lawns and gardens. The scenario assumes that dry pesticide materials (pellets and granules) are ingested by children who play in treated areas (e.g., lawns, playgrounds). However, that scenario is not appropriate for naphthalene due to its unique use directions and application methods. For naphthalene, EPA selected episodic ingestion of naphthalene flakes applied indoors as the episodic ingestion scenario that would lead to the most potential exposure. Episodic ingestion of naphthalene mothballs or granules was considered to have a lower likelihood of exposure because the mothballs are contained in sachets, or the granules must be placed inside cheese cloths, panty hoses, etc. and hung in less-accessible areas such as attics. Naphthalene granules for outdoor use were not considered in the episodic ingestion scenario as children are less likely to access the types of outdoor areas where naphthalene is labeled for use (i.e., the perimeter of wood piles, trash cans, flower beds, etc.) than they are to access the naphthalene flakes applied indoors in closets. Therefore, a screening level calculation was conducted for the episodic ingestion of naphthlene flakes. Using the POD of 400 mg/kg/day with an uncertainty factor of 1000, for a 15 kg child, a dose of 0.006 grams or 0.00021 oz of naphthalene is needed to get an MOE of 1000. Therefore, if a child consumed more than 0.006 g or 0.00021 oz of flakes, there would be risk estimates of concern.

Aggregate (Combined) Risk Assessment

Food Quality Protection Act (FQPA) considerations do not apply to naphthalene for the currently registered (non-food) use patterns; no exposure to naphthalene is expected from food based on the registered use patterns. Although there are potential exposures from drinking water (oral exposure) and from residential uses (inhalation exposure), those exposures are not combined since the PODs for the oral and inhalation exposures are not based on common toxicological

effects. Episodic oral exposures are not combined with dietary drinking water exposures as the episodic exposure is considered a sporadic, one-time exposure.

Non-Occupational Spray Drift Assessment
A quantitative spray drift assessment was not conducted because the registered uses of naphthalene for treatment in indoor residential environments and outdoor areas are not anticipated to be a source of spray drift.

Occupational Exposure and Risk Assessment
Short-term inhalation risk estimates of concern were identified for occupational handlers (MOE < LOC; LOC = 30). MOEs range from 0.0042 to 1.9 for indoor applications of naphthalene flakes and granules, respectively. No risks of concern were identified for the application of granules to outdoor environments; MOE = 150 (LOC = 30). Intermediate-term inhalation risk estimates of concern were identified for occupational handlers (MOE < LOC; LOC = 30). MOEs range from 0.0017 to 0.76 for indoor applications of naphthalene flakes and granules, respectively. No risks of concern were identified for the application of naphthalene granules to outdoor environments; MOE = 61 (LOC = 30). Occupational handler dermal exposures were not assessed since a dermal endpoint was not selected. Occupational post-application exposures are not expected, as occupational handlers who apply naphthalene products in a residential setting would not be expected to remain in that residential setting for a time period sufficient to result in significant exposure.

Environmental Justice
Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations.[1]" (see Section 3.5.)

Human Studies Review
This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from the Residential SOPs (Lawns/Turf, Indoor), are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found on the EPA website[2].

2.0 Risk Assessment Conclusions

There are no dietary risk estimates of concern.

[1] https://www.epa.gov/laws-regulations/summary-executive-order-12898-federal-actions-address-environmental-justice

[2] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure

Inhalation risk estimates of concern were identified for residential handlers applying naphthalene flakes and granules indoors indoors. Inhalation risk estimates were not of concern for residential handlers applying naphthalene granules outdoors. All short-, intermediate-, and long-term residential post-application inhalation scenarios result in risk estimates of concern. The episodic ingestion scenario results in risk estimates of concern.

Inhalation risk estimates of concern were identified for occupational handlers applying naphthalene flakes and granules indoors.

2.1 Data Deficiencies

None.

2.2 Label Recommendations

None.

2.2.1 Recommendations from Residue Reviews

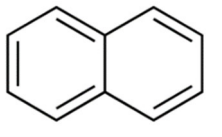
None.

2.2.2 Recommendations from Residential and Occupational Assessment

HED recommends all registered labels to specify a rate for the application of all naphthalene products to both indoor and outdoor areas. In addition, HED has identified risk estimates of concern for the residential handler, residential post-application, episodic ingestion, and occupational handler scenarios. HED recommends appropriate mitigation to be put in place for risks of concern identified in this assessment.

3.0 Introduction

3.1 Chemical Identity

Table 3.1 Test Compound Nomenclature	
Chemical Structure	
Empirical Formula	$C_{10}H_8$
Common Name	Naphthalene
Company experimental name	Naphthalene
IUPAC name	Naphthalene
CAS Name	Naphthalene
CAS Registry Number	91-20-3; 68412-25-9
End-use product/EP	Mothballs, Flakes, Granules
Chemical Class	Fumigant Insecticides
Known Impurities of Concern	N/A

3.2 Physical/Chemical Characteristics

Naphthalene is a white crystalline volatile solid with a strong coal-tar odor. Open literature data indicate that naphthalene can bind relatively rapidly to soils with a sustained desorption of days to weeks. These data also indicate that it degrades with aerobic soil metabolism half-lives between 3.5 and 40 days with no appreciable degradation under anaerobic conditions. Naphthalene is insoluble in water. Naphthalene has a reported vapor pressure of 0.085 mm Hg @ 25°C which indicates it is volatile with a likelihood for exposure in the vapor phase. It has a Log K_{OW} = 3.3 indicating t has a lipophilic nature. A detailed summary of the physical/chemical characteristics of naphthalene is presented in Appendix B.

3.3 Pesticide Use Pattern

Naphthalene is used for moth treatment for the protection of woolen clothing (indoor) and as an animal repellant against nuisance vertebrate pests (indoor and outdoor). Registered products for use within the home are formulated as mothballs, granules, or flakes. All mothball products are sold in sachets.[3] The naphthalene flake product (for indoor use) is packaged as loose flakes. The indoor and outdoor granule products are sold either in repellent stations or as loose granules. All products contain 99.85-99.95% active ingredient.

Table 3.3. Summary of Directions for Use of Naphthalene

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate[1] (lb ai/ft^3)	Max. No. Applic. per Year	Max. Seasonal Applic. Rate (lb ai/ft^3)	Use Directions and Limitations
Indoor					
Hand Application	Mothball [1475-75 (moth flakes); 1475-74; 1475-163; 1475-120; 81433-6] 99.85-99.95% ai	0.02	N/S	N/S	Keep out of reach of children. Do not place in areas accessible to children. Do not use dry cleaning bags, garbage bags, or other containers that allow vapors to escape into unoccupied rooms. Do not mix naphthalene or use it together with other moth preventative chemicals. Apply product in clean, airtight containers, bags and closets. Keep product in airtight space for a minimum of seven (7) days. Replenish product that has dissipated; moths are active all year.
	Repellant Station; Granule [1475-160; 58630-2] 99.95% ai	0.0025			EPA Reg No. 1475-160: Keep out of reach of children. Do not place in areas accessible to children. Remove repellant stations from package and place one hand on the top section of the station and the other hand on the bottom section. To activate the station, pull the two sections away from each other until they click

[3] There is one currently-registered naphthalene mothball product (EPA Reg. No. 91974-2) that has loose mothballs, not contained in sachets. Sachets were required for all mothball products by the naphthalene 2008 Reregistration Eligibility Decision). This product is in the process of being voluntarily cancelled by the registrant. The Federal Register Notice (FRN) announcing receipt of the request to cancel this product was published on July 10, 2018. A FRN announcing the final cancellation order is expected to publish in 2019.

Table 3.3. Summary of Directions for Use of Naphthalene					
Applic. Timing, Type, and Equip.	**Formulation [EPA Reg. No.]**	**Applic. Rate[1] (lb ai/ft^3)**	**Max. No. Applic. per Year**	**Max. Seasonal Applic. Rate (lb ai/ft^3)**	**Use Directions and Limitations**
					into position. Place stations or use optional wires to hang or stand the stations in areas as specified by the label. Place stations in accessible areas of attics and wall voids so that they can be easily removed if the odor becomes too strong. EPA Reg. No. 58630-2: Do not apply the product directly in the attic or wall void. Place in mesh bag, cheese cloth, panty hose or small, open topped cardboard container so that the product can be easily removed if the odor becomes too strong.
Outdoor					
Hand Application	Repellant Station [1475-160] 99.95% ai	0.0025	N/S	N/S	Keep out of reach of children. Do not place in areas accessible to children. Remove repellant stations from package and place one hand on the top section of the station and the other hand on the bottom section. To activate the station, pull the two sections away from each other until they click into position. Place stations or use optional wires to hang or stand the stations in areas as specified by the label.
	Granule [58630-1; 58630-2] 99.95% ai	N/S	N/S	0.00025[2]	Ornamentals: Apply one or more-inch-wide band of product around the plant. Do not apply directly to foliage or stems. Hot weather and wind will necessitate more frequent applications. All other outdoor areas; areas around houses, cabins, trailers, garages, utility houses, barns, woodpiles, sand piles, trash cans, flower beds, garbage bags placed near residences and other buildings, or to garbage bags placed along streets or alleys for garbage collection. Apply product using bands 4 to 5 inches wide for garter snakes and 8 to 12 inches wide for rattlesnakes. In yards, lightly sprinkle over the area within the treatment band. To control rats and mice apply in a lightly sprinkled band area where garbage bags are placed; begin from one foot out and lightly broadcast until band of product is 24 inches wide. Do not apply this product in gardens or in fields of crops grown for food or feed. Do not use this product near streams, ponds, pools, and water supplies.

[1] ((lb product)/(ft^3 treated))*(% ai)) = lb ai/ft^3

[2] Maximum application rate from Environmental Fate and Effects Division (EFED) Drinking Water Memo (M. Corbin, D351119, 04/09/2008); (10.8 lb/A)*(1A/43560 ft^2)

3.4 Anticipated Exposure Pathways

Since there are no food uses for naphthalene, exposure from food will not occur. However, humans may be exposed to naphthalene in drinking water since it is applied outdoors as a narrow band around target areas to be protected (houses, barns, wood piles, trash cans, flower beds, etc). Residues of naphthalene could potentially reach drinking water through run-off from this type of outdoor application. Residential handler exposures are expected, and adults may be exposed to naphthalene during indoor and outdoor applications in residential settings. Post-application inhalation exposures are also expected since adults and children may be exposed to volatilized naphthalene after indoor applications in residential settings. There also is the potential for episodic ingestion by children. The naphthalene products that are formulated as mothballs are in required packaging (i.e. sachets), which are expected to decrease the potential for incidental ingestion. However, there are granule and flake products that allow for loose application indoors. Other granule products are either labelled for indoor application to wall voids and attics or outdoor application around houses, cabins, trailers, garages, utility houses, barns, woodpiles, sand piles, trash cans, and flower beds/ornamentals to repel nuisance vertebrate pests. There is the potential for children to encounter naphthalene when it is applied loosely in accessible areas, such as closets. Incidental oral (hand to mouth) exposures are not expected. Incidental oral scenarios describe a child contacting a surface with residue from a treatment. In the case of naphthalene, the non-dietary oral exposure scenario that is most likely to occur is from naphthalene flake ingestion. There is no spray or residues for a child to contact. While there may be potential for residential post-application dermal exposure, a residential post-application dermal assessment was not conducted since a dermal endpoint was not selected. Exposures resulting from non-occupational spray drift or off-field bystander volatilization are not expected based on the formulation of naphthalene and how it is applied.

Occupational handler exposures are expected, and occupational handlers may be exposed to naphthalene during indoor and outdoor applications in residential settings. Occupational post-application exposures are not expected, as occupational handlers who apply mothball products in a residential setting would not be expected to remain in that residential setting for a time period sufficient to result in significant exposure.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (https://www.archives.gov/files/federal-register/executive-orders/pdf/12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America,

(NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are also currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to other types of possible bystander exposures and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

4.1 Toxicology Studies Available for Analysis

The naphthalene toxicity database is complete; the Hazard Science Policy Council (HASPOC) recommended waiving a two-generation reproductive toxicity study via the inhalation route (the primary route of human exposure) (TXR# 0057813, 11/01/2018). An updated literature search was performed for naphthalene and produced no studies that would impact the risk assessment (see Appendix D for the literature search sources, search parameters and number of articles identified).

The database includes the following studies:

- Subchronic toxicity - oral: rat and mouse National Toxicology Program (NTP) studies[4]
- Developmental toxicity - oral: rat and rabbit NTP studies
- 4-week and 90-day toxicity inhalation: rat
- Combined chronic toxicity/carcinogenicity – inhalation: rat and mouse NTP studies
- Acute Neurotoxicity – oral: rat
- Subchronic Neurotoxicity – inhalation: rat
- Dermal toxicity: rat
- Other: mutagenicity battery
- Metabolism: rat
- Immunotoxicity: mouse

4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

There are no guideline ADME studies available. However, there is an open literature study (Bakke et al. 1985)[5] on the oral absorption of radiolabeled naphthalene in Sprague-Dawley rats. In this study, radiolabeled naphthalene (dissolved in ethanol) was administered orally (no further

[4] NTP. 1980a. Subchronic toxicity study: Naphthalene (C52904), B6C3F1 mice. Research Triangle Park, NC: U.S. Department of Health and Human Services, National Toxicology Program.
NTP. 1980b. Subchronic toxicity study: Naphthalene (C52904), Fischer 344 rats. Research Triangle Park, NC: U.S. Department of Health and Human Services, National Toxicology Program.

[5] Bakke J et al. 1985. Catabolism of premercapturic acid pathway metabolites of naphthalene to naphthols and methylthio-containing metabolites in rats. Proc Natl Acad Sci USA 82: 668-671.

details) to 2 groups of control rats (no bile duct cannulation) and to 4 groups of bile duct cannulated rats, and radioactivity was measured in urine, feces, and bile collected for 72 hours. In the 2 control groups, recovery of radioactivity was reported as: 81.1% and 84.3% (urine), 6.3% and 6.6% (feces). Radioactivity in the carcasses accounted for 2.6% and 6.6% of the administered dose. Bile cannulation data revealed significant enterohepatic circulation. In the bile cannulated rats, radioactivity accounted for 27.4 to 34.2% in urine and 58.5 to 75.2% in bile. Recovery of radioactivity in the feces was less than 1% in 3 groups and less than 2% in the 4th group. No radioactivity was detected in 3 groups, and 0.2% in the 4th group. The results of this study demonstrate that naphthalene is well absorbed following the oral route.

A literature study by Buckpitt et al. (2002)[6] examined the metabolism of naphthalene. Naphthalene undergoes oxidative metabolism by cytochrome P-450 oxygenases resulting in the epoxide 1,2-napthalene oxide. The epoxide can spontaneously hydrolyze to naphthols, and then form glucuronic acid or sulfate conjugates. Alternatively, the epoxide can be conjugated with glutathione, as mediated by glutathione-S-transferase. Through several steps, the glutathionyl conjugates are converted to mercapturic acids. The epoxide can also be enzymatically hydrated by epoxide hydrolase to form 1,2-dihydorxy-1,2-dihydronaphthalene. The latter compound can then undergo further reactions (catechol reduction followed by oxidation) to form 1,2-naphthoquinone. Figure 1 below depicts the metabolism of naphthalene and its potential role in the toxicity of naphthalene.

[6] Buckpitt A et al. 2002. Naphthalene-induced respiratory tract toxicity. Metabolic mechanisms of toxicity. Drug Metab Rev 34(4):791-820.

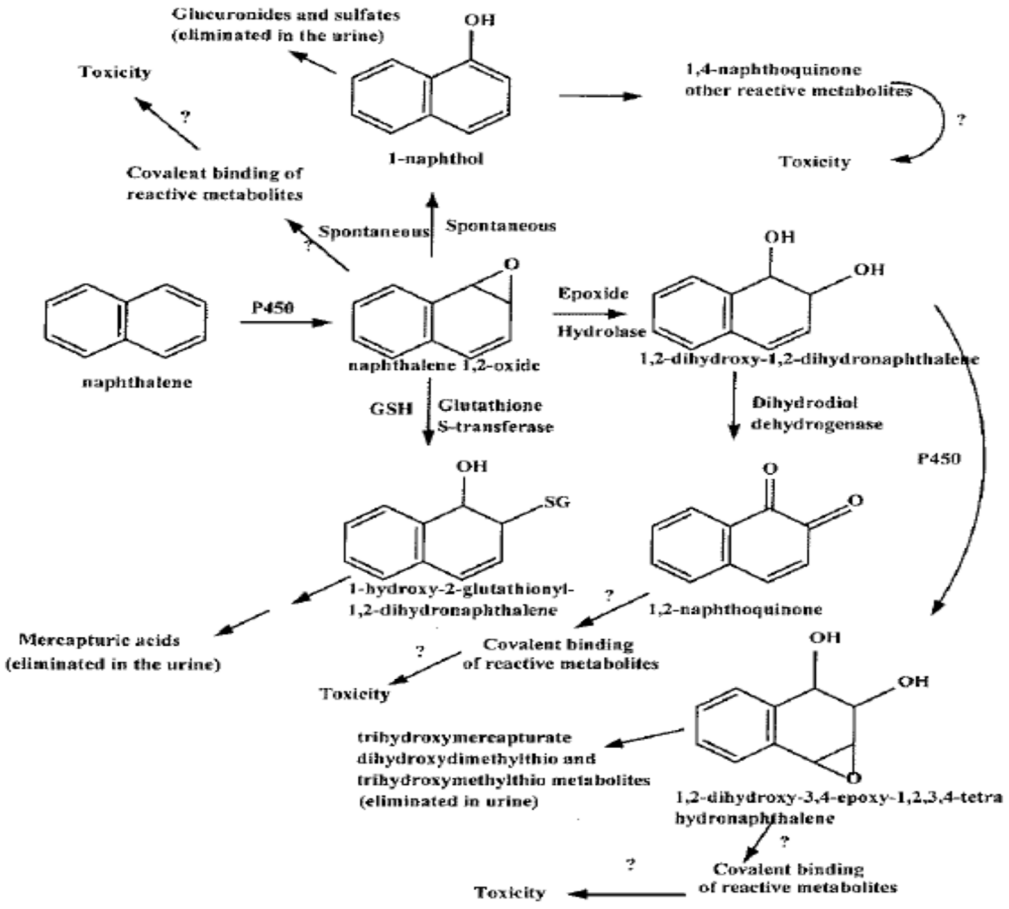


FIGURE 1. Naphthalene Metabolism and Formation of Reactive Metabolites (Source: Buckpitt 2002)

4.2.1 Dermal Absorption

There is no guideline dermal absorption study on naphthalene. However, a dermal absorption factor is not needed because a dermal endpoint was not selected, and dermal exposure is anticipated to be negligible.

4.3 Toxicological Effects

In an NTP subchronic oral (gavage; vehicle corn oil) rat study (NTP 1980), toxicity was manifested as decreased body weights in males and females and histological lesions of the kidney (minimal cortical tubular degeneration) were observed in males. In the NTP subchronic oral (gavage) mouse study (NTP 1980), exposure resulted in lethargy at weeks 3 and 4. A published 90-day study in the mouse (Shopp et al. 1984) reported significant decreases in brain, liver, and spleen weights in females only at a high dose; but histological examinations were not performed to assess the toxicological significance of these changes. In addition, these effects were not observed in the NTP subchronic oral study which tested higher dose levels than the Shopp et al. study and included thorough histopathological examinations. There are no chronic oral toxicity studies available in any species.

Short- and long-term inhalation toxicity studies (4- and 13-week nose-only in the rat and 2-year chamber in the rat and mouse) indicated that naphthalene is a nasal toxicant at low concentrations. Nonneoplastic findings in the nasal cavity included atrophy and degeneration of the olfactory epithelium, loss of Bowman's glands, hypertrophy of the respiratory epithelium and fusion of turbinates. The results of the 2-year inhalation studies in the rat and mouse revealed that severities of the lesions increased with increasing exposure concentrations and durations. There are some data that have indicated differences in the metabolism and consequent potential species susceptibility to naphthalene (Buckpitt et al. 1992; 1995; Baldwin et al. 2004)[7]. In particular, the data indicate that rodents may be more sensitive than humans with regard to respiratory toxicity. This difference in sensitivity is based on the considerably lower levels of cytochrome P-450 enzymes and significantly lower metabolism of naphthalene to the epoxide in humans (obligatory first step in toxicity).

Some evidence of neurotoxicity was noted in the developmental oral and ACN oral studies in rats, as well as the subchronic oral rat and mouse studies. In the ACN study, clinical signs (piloerection, fast respiration, hunched posture), reduced motor activity, lower body temperature, head shaking, and increased urination and defecation in the open field were observed at 400 mg/kg. Neurotoxicity following subchronic oral (gavage) exposure included lethargy in rats (at 400 mg/kg/day - the highest dose tested) and mice (200 mg/kg/day), and hunched posture in rats (400 mg/kg/day). Persistent clinical signs of lethargy, slow breathing, and rooting behavior were noted in dams in the developmental rat study at 150 mg/kg/day. The clinical signs of neurotoxicity in the oral studies may be attributed to high dose gavage administration of naphthalene. There were no changes in brain weight or neurohistopathological effects in any of the studies by either oral or inhalation routes of exposure in the well-conducted NTP studies that included thorough histopathology. Inhalation toxicity studies indicate loss of olfactory neurons in rats.

In a 90-day dermal toxicity study in the rat, effects were noted only at the high dose of 1,000 mg/kg/day. These effects included an increased incidence and severity of excoriated skin and papules in both sexes; atrophy of seminiferous tubules in the males; and nonneoplastic lesions in the cervical lymph node (hyperplasia), liver (hemosiderosis), thyroid (thyroglossal duct cysts), kidneys (pyelonephritis), urinary bladder (hyperplasia) and skin (acanthosis, hyperkeratosis) in females.

There was no evidence of increased susceptibility (quantitative or qualitative) of rat or rabbit fetuses to *in utero* exposure to naphthalene. The HASPOC recommended waiving a two-generation reproductive toxicity inhalation study in the rat (TXR# 0057813, 11/01/2018); the

[7] Buckpitt AR et al. 1992. Relationship of cytochrome P450 activity to cell cytotoxicity. II. Comparison of stereo-selectivity of naphthalene epoxidation in lung and nasal mucosa of mouse, hamster, rat and Rhesus monkey. J Pharmacol Exp Ther 261: 364-372.
Buckpitt AR et al. 1995. Relationship of cytochrome P450 activity to cell cytotoxicity. IV. Metabolism of naphthalene and naphthalene oxide in microdissected airways from mice, rats, and hamsters. Molecular Pharmacol 47:74-81.
Baldwin RM, Jewell WT, Fanucci MV, Plopper C, Buckpitt A. (2004). Comparison of pulmonary/nasal CYP2F expression levels in rodents and rhesus macaque. J Pharmacol Exp Ther 309:127–136.

rationale was based on the lack of histological effects on male and female reproductive organs seen in the available database, and nasal lesions being likely the most sensitive target of toxicity.

In chronic inhalation studies, carcinogenic effects have been observed in both rats and mice following inhalation exposure (se Section 4.5.3). Findings include nasal tumors in rats, liver tumors in male mice, and tumors of the lung in female mice. The carcinogenic potential of naphthalene is currently undergoing review by EPA's NCEA. EPA's Health Effects Division has not performed a quantitative cancer risk assessment for naphthalene.

Based on the overall review of the database (including gene mutation, chromosomal aberrations, unscheduled DNA studies), it is concluded that naphthalene does not act as a direct DNA reactive mutagen.

In contrast to rodents, humans are susceptible to the hemolytic effects of naphthalene exposure. In humans, hemolytic anemia is the most commonly reported manifestation of naphthalene exposure (U.S Department of Health and Human Services' Agency for Toxic Substances and Disease Registry (ATSDR) 2005). Infants and individuals deficient in glucose-6-phosphate dehydrogenase (G6PDH) are particularly sensitive to naphthalene-induced hemolytic anemia. Symptoms associated with naphthalene-induced anemia include hemolysis, decreased hemoglobin and hematocrit levels, increased reticulocyte counts, serum bilirubin levels, Heinz bodies, fatigue, lack of appetite, restlessness, and pale appearance (ATSDR 2005). Although human data are inadequate to assess a dose-response relationship for hemolytic anemia and factors such as time to peak effect, cases of hemolytic anemia are typically associated with exposure to large amounts of naphthalene, often from misuse of the product (i.e., ingestion of mothballs and following inhalation to excessive amounts of mothballs). For example, in one case report, a 16-year-old girl swallowed 6 g of naphthalene and exhibited hemolytic anemia (Gidron and Leurer 1956; cited in ATSDR 2005). While hemolytic anemia has not been observed in rats or mice, there is a study (Zuelzer and Apt 1949, cited in ATSDR 2005) that reported hemolytic anemia in a dog receiving a single 1,525 mg/kg dose of naphthalene in food and in another dog receiving approximately 263 mg/kg/day for 7 days in food.

4.4 Consideration for Toxicity to Children[8]

Naphthalene is a non-food use chemical; therefore, requirements of the FQPA do not apply. However, this assessment considers potential increased susceptibility of infants, children, and fetuses (as a result of exposure to women of child-bearing age) from exposure to naphthalene taking into account the completeness of the toxicity and exposure databases and the potential for pre- and post-natal toxicity.

4.4.1 Completeness of the Toxicology Database

The existing toxicological database for this non-food use chemical is adequate for characterizing any potential for prenatal susceptibility for infants and children. Available naphthalene studies for evaluation of prenatal susceptibility include developmental studies in the rat and rabbit. A

[8] HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (https://www.epa.gov/children/epas-policy-evaluating-risk-children).

two-generation reproductive toxicity inhalation study in the rat was not required (TXR# 0057813, 11/01/2018); the HASPOC rationale was based on the lack of histological effects on male and female reproductive organs in the available database, and nasal lesions are likely the most sensitive indication of toxicity.

4.4.2 Evidence of Neurotoxicity

There is evidence of neurotoxicity in the developmental oral and ACN oral studies in rats, as well as the subchronic oral and inhalation rat and mouse studies (see Section 4.3); however, concern is low since: 1) effects are well-characterized with clearly established NOAEL/LOAEL values; 2) neurotoxicity observed in several oral studies was likely attributed a to high dose bolus gavage administration in the oral toxicity studies; and 3) the selected endpoints for risk assessment are protective of these effects.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

There was no evidence of increased susceptibility (quantitative or qualitative) of rat or rabbit fetuses to *in utero* exposure to naphthalene. A two-generation reproductive toxicity inhalation study in the rat was not required at this time (TXR# 0057813, 11/01/2018).

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties in the exposure database. Adequate exposure data are available to assess the residential and occupational exposure resulting from the registered uses; these data will not underestimate exposure to naphthalene. Drinking water exposure was determined using high-end modeled estimates of residue concentrations.

4.5 Toxicity Endpoint and Point of Departure Selections

Based on the use pattern and the toxicological profile of naphthalene, endpoints were selected for acute and chronic dietary risk assessment and for assessing potential risks associated with occupational and non-occupational inhalation exposures. The endpoints for naphthalene have been revised since the previous assessment, the HED chapter of the Reregistration Eligibility Document (D335946, D. Drew et. al., 02/28/2008); previously a quantitative assessment for inhalation was not conducted. In the 2008 naphthalene RED, inhalation exposures were not quantitatively assessed because of the issue of potential species differences with respect to respiratory toxicity and metabolism. Although standard inhalation rodent toxicity studies are available, some mechanistic studies have raised the issue of potential species differences (with regard to respiratory toxicity and metabolism) and the applicability of the rodent model as a default approach to estimate human risk following inhalation exposures to naphthalene. Instead, the inhalation toxicity hazards were characterized and then directly compared with anticipated human exposure to naphthalene with 1) the doses found to result in no adverse effects in rodents (NOAELs) and 2) the doses found to result in toxic outcomes in rodents (LOAELs). However, a mode of action (MOA) analysis consistent with the EPA weight-of-evidence framework guidance was not submitted to the agency to definitively support species differences in mode of

action of naphthalene with regard to respiratory toxicity. Therefore, a quantitative assessment of inhalation is included in the current assessment.

4.5.1 Dose-Response Assessment

Acute Dietary Endpoint for the General Population (including Infants and Children): The study used for establishing the aRfD for the general population was the ACN oral study in rats. Effects at the LOAEL of 400 mg/kg included hunched posture in females, head shaking in males and females, and reduced motor activity in males and females. A NOAEL was not identified. This study is appropriate for the duration of exposure and is protective for the general population (including infants/children). An acute reference dose (aRfD) of 0.4 mg/kg/day was derived from a LOAEL of 400 mg/kg/day and a 1000-fold UF (10X for inter-species extrapolation, 10X for intra-species variation, and a 10X factor for LOAEL to NOAEL extrapolation).

Chronic Dietary Endpoint for All Populations: The study used for deriving the chronic reference dose (cRfD) was an NTP subchronic oral toxicity study in the rat (1980a). The LOAEL of 200 mg/kg/day is based on significant decreases in body weights. The NOAEL is 100 mg/kg/day. This study is appropriate for the duration of exposure and protective of the populations of concern. The cRfD of 0.1 mg/kg/day was derived from a NOAEL of 100 mg/kg/day and a 1000-fold UF (10X for inter-species extrapolation, 10X for intra-species variation, and a 10X for subchronic to chronic extrapolation).

Dermal, Short- and Intermediate-Term: A dermal endpoint for risk assessment was not selected for naphthalene. No effects were noted at 300 mg/kg/day following subchronic exposure of rats via the dermal route. In addition, dermal exposure to naphthalene is minimal.

Inhalation, Short- Term (1-30 days): The short-term inhalation endpoint was derived from the route-specific 4-week (nose-only) inhalation study in rats (MRID 42934901) where the NOAEC is 3 ppm (0.017 mg/L). The effects observed at the portal of entry LOAEC of 10 ppm (0.055 mg/L) consisted of an increased incidence and severity of nasal lesions (slight disorganization, rosette formation, basal cell hyperplasia, erosion, atrophy, and degenerate cells in the olfactory epithelium; loss of bowman's glands; respiratory epithelium hypertrophy; rosette formation in the septal organ of Masera and fusion of the turbinates). This study is appropriate for short-term inhalation exposure for adults and children in occupational and residential settings.

Human-equivalent concentrations (HECs) for residential and occupational scenarios were derived using the NOAEC and the regional gas deposition ratio (RGDR). The RGDR is the animal-to-human ratio of minute ventilation (V_E) normalized to unit surface area (SA) of the respiratory tract region being affected. Human equivalent concentration (HEC) and dose (HED) calculations are summarized in Tables 4.5.4.2 to 4.5.4.7.

A total uncertainty factor of 30X is appropriate (3X for interspecies extrapolation, 10X for intraspecies variation), resulting in a LOC of 30X. A total uncertainty factor of 30X is appropriate (3X for interspecies extrapolation, 10X for intraspecies variation), resulting in a LOC of 30X. A full interspecies factor of 10X could be reduced because the RfC methodology developed by EPA was followed in which dosimetry adjustments were used to derive a NOAEC

(HEC), which accounts for the pharmacokinetics component of the interspecies extrapolation, thus allowing a reduction of the interspecies factor from 10X to 3X.

Inhalation, Intermediate-Term: The intermediate-term inhalation endpoint was derived from the subchronic (nose-only) neurotoxicity (SCN) rat study (MRID 44856401). The LOAEC of 10 ppm (analytically verified as 0.052 mg/L) was based on portal of entry effects including atrophy/disorganization of the olfactory epithelium and hyperplasia of the respiratory and transitional epithelium. The NOAEC was 1 ppm (analytically verified as 0.005 mg/L). The SCN study is supported by the findings of the 90-day (nose-only) inhalation study in rats (MRID 42835901) where the minimal LOAEC was 2 ppm (analytically verified as 0.011 mg/L) based on portal of entry effects (minimal severity) including increased incidence of nasal lesions (degeneration, atrophy and hyperplasia of basal cells of the olfactory epithelium; rosette formation of olfactory epithelium; loss of Bowman's glands; hypertrophy of respiratory epithelium).

A total uncertainty factor of 30X is appropriate (3X for interspecies extrapolation, 10X for intraspecies variation), resulting in a LOC of 30X.

Inhalation, Long-Term: The long-term inhalation endpoint was selected from a chronic toxicity and carcinogenicity study in the rat (NTP 2000). The LOAEC of 10 ppm (0.052 mg/L) was based on increased incidence and severity of atypical (basal cell) hyperplasia, atrophy, chronic inflammation, and hyaline degeneration of the olfactory epithelium; hyperplasia, squamous metaplasia, hyaline degeneration, and goblet cell hyperplasia of the respiratory epithelium; and glandular hyperplasia and squamous metaplasia. A NOAEC was not identified.

Human-equivalent concentrations for residential and occupational scenarios were derived using the LOAEC and the regional gas deposition ratio (RGDR). The RGDR is the animal-to-human ratio of minute ventilation (V_E) normalized to unit surface area (SA) of the respiratory tract region being affected. For the chronic carcinogenicity inhalation toxicity study in the rat (NTP 2000), an RGDR of 0.208 was estimated. HEC and HED calculations are summarized in Table 4.5.4.4.

A total uncertainty factor of 300X is appropriate (3X for interspecies extrapolation, 10X for intraspecies variation, and a 10X factor for extrapolating a LOAEC to NOAEC).

Inhalation and Oral Hazard Characterization and Hemolytic Anemia

Since the adoption of recent risk mitigation efforts aimed at reducing oral exposures (e.g., repackaging of mothball products into sachets and inclusion of precautionary language), incidents related to children's oral ingestion have been greatly reduced. Inhalation exposure remains the primary route of exposure to naphthalene. The inhalation PODs are conservative because they are based on very sensitive portal-of-entry effects in the rat. Portal-of-entry effects involve direct contact of naphthalene with the respiratory tract. Moreover, there is some evidence that rats may be more sensitive than humans to the naphthalene respiratory effects (see section 4.3).

While there is some uncertainty concerning hemolytic anemia following naphthalene exposure, most human case reports reflect excessive and often inappropriate use of naphthalene products (i.e. mothballs, flakes, and granules), including accidental ingestion (primarily by children), intentional ingestion (maternal pica), intentional sniffing (inhalation drug abuse), inappropriate off-label uses, and excessive use that results in elevated air concentrations of naphthalene.

Excessive use of naphthalene mothball products can result in elevated air concentrations of the chemical. For example, the Centers for Disease Control and Prevention (CDC)[9] reported an incident of exposure to high (misuse) levels of naphthalene (300 – 500 mothballs) within a home including living quarters (i.e., kitchen, living room). Reported symptoms included headache, nausea, vomiting, abdominal pain, malaise, confusion, icterus, renal disease and anemia. Most symptoms disappeared after mothball use was discontinued. A level of approximately 20 ppb (approximately 0.1 g/m^3) in the home was measured after remediation and likely underestimated actual exposure. Application of an exposure model that estimates potential long-term (period of one year) average indoor air (residential) levels indicate levels of approximately 0.0771 to 1.289 mg/m^3 could be associated with use of 300 – 400 mothballs based on EPA's Exposure Factors handbook estimate of a volume of 492 m^3 for a residential home, These concentrations reflect levels associated with misuse scenarios (.010 – 0.3 mg/m^3; Price and Jayjock, 2008)[10].

Based on the following WOE approach and considering all of the available hazard and exposure information for naphthalene, HED is confident that the current proposed endpoints are protective of potential hemolytic anemia:

1. Nasal lesions (i.e., hyperplasia and metaplasia in respiratory and olfactory epithelium) would likely remain as the most sensitive indication of toxicity and are protective of hemolytic anemia following inhalation exposure;
2. Dog studies show hemolytic anemia occurring at 74 mg/kg/day following 7 days of exposure, approximately 480-fold, 1500-fold, and 1400-fold higher than the POD being used for ST, IT, and LT inhalation endpoints (0.16 mg/kg/day, 0.05 mg/kg/day, and 0.05 mg/kg/day oral human equivalent doses), respectively; and 185 to 740 higher than PODs used for acute and chronic dietary exposures.
3. Human incident data show potential hemolytic anemia occurring in a child who ate ¼ mothball (approximately 125-1250 mg). Assuming the child weighed 10 kg, this corresponds to an acute oral dose of 12.5-125 mg/kg – approximately 80- to 800-fold higher than the POD used for the ST endpoint;
4. The potential hemolytic anemia occurring in a child who ate ¼ mothball is also at a level 5700-fold higher than what a child would breathe from vapors based on the inhalation concentrations from the chemical specific air concentration study.
5. A family (children and adults) exposed via inhalation to approximately 300-500 mothballs (used throughout the house, likely misuse) over a long-term duration showed symptoms of hemolytic anemia. Estimated indoor air concentrations from this use range from 77-1290 ug/m^3, approximately 9- to 143-fold higher than the maximum allowable

[9] https://www.cdc.gov/mmwr/preview/mmwrhtml/00001236.htm
[10] Price PS, Jayjock MA. 2008. Available data on naphthalene exposures: strengths and limitations. Regul Toxicol Pharmacol. 51: S15-21.

air concentration for long-term exposure based on respiratory lesions. Eight-hour average air concentrations found in a chemical-specific naphthalene monitoring study in which mothballs were placed in drawers and closets, as per label directions, were 36 ug/m^3, approximately 2- to 35-fold lower than estimated air concentrations when mothballs were distributed throughout the house; and

6. OSHA TLV (threshold limit value) and STEL (short-term exposure limit) values (values summarized in table below) range from 2800- to 8800-fold higher than the maximum allowable air concentrations determined by HED based on nasal lesions. The OSHA values are protective of sensitive eye irritation in humans. OSHA also lists hemolytic anemia as a hazard concern for naphthalene.

Table 4.5.1. EPA/OPP and OSHA Comparison

Agency	Scenario	Population	Limit (ug/m^3)	Safety factor	Adjusted maximum acceptable air concentration (ug/m^3)
EPA/OPP	ST	Adults	834	30	28
		Children 1-2	741	30	25
	IT	Adults	245	30	8
		Children 1-2	218	30	7
	Long term	Adults	2899	300	10
		Children 1-2	2577	300	9
OSHA	ACGIH TLV - Chronic	Adults	50,000	1	50000
	ACGIH STEL - ST	Adults	79,000	1	79000

4.5.2 Recommendation for Combining Routes of Exposures for Risk Assessment

As part of conducting a human health risk assessment, HED considers risks from individual routes of exposure (oral, dermal, and inhalation). Additionally, HED must assess combined risks from dietary and residential (non-occupational) exposures. In order to conduct a combined risk assessment, a determination is made if it is appropriate to combine across routes of exposure and combine dietary risks with residential (non-occupational) risks. Based upon different effects and/or target organs observed in the selected endpoints for the naphthalene risk assessment, oral and inhalation routes of exposure should not be combined.

4.5.3 Cancer Classification and Risk Assessment Recommendation

In chronic studies, carcinogenic effects have been observed in both rats and mice following inhalation exposure. In the rat study (inhalation), nasal tumors included neuroblastomas of the olfactory epithelium and adenomas of the respiratory epithelium. In the mouse study (inhalation), male mice had statistically significant increased incidences of liver adenomas, and adenomas and carcinomas combined. Female mice exhibited increased incidences of alveolar/bronchiolar adenomas, and adenomas and carcinomas combined. The carcinogenic potential of naphthalene is currently undergoing review by EPA's NCEA.

There are some data that suggest differences in the metabolism and potential species susceptibility to naphthalene (Buckpitt et al. 1992; 1995).

4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.4.1 Summary of Toxicological Doses and Endpoints for Naphthalene for Use in Dietary, Non-Occupational and Occupational Human Health Risk Assessments.

Exposure/ Scenario	POD	Uncertainty Factors	RfD, PAD, LOC for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All populations)	LOAEL = 400 mg/kg/day	UF_A= 10x UF_H = 10x UF_L= 10x	aRfD= 0.4mg/kg/day	**Acute Oral Neurotoxicity Study - Rat** MRID 44282801 NOAEL = not identified. LOAEL = 400 mg/kg/day based on hunched posture in females, head shaking in males and females, and reduced motor activity in males and females.
Chronic Dietary (All populations)	NOAEL= 100 mg/kg/day	UF_A= 10x UF_H = 10x UF_S = 10x	cRfD = 0.100 mg/kg/day	**NTP Subchronic Rat Study (**1980a) NOAEL = 100 mg/kg/day LOAEL = 200 mg/kg/day based on significant decreases in body weights and renal effects (minimal cortical focal lymphocytic infiltrate; focal tubular regeneration).
Dermal Short- (1-30 days) and Intermediate-Term (1-6 months)	A dermal endpoint for risk assessment was not selected.			
Inhalation (Short-Term; 1-30 days)	NOAEC = 3 ppm For HEC and HED calculations see Table 4.5.4.2 to 4.5.4.7	UF_A = 3x UF_H = 10x	LOC = 30	**4-Week (Nose-Only) Inhalation – Rat** MRID 42934901 LOAEC = 10 ppm based on increased incidence and severity of nasal lesions (slight disorganization, rosette formation, basal cell hyperplasia, erosion, atrophy, and degenerate cells in the olfactory epithelium; loss of bowman's glands; respiratory epithelium hypertrophy; rosette formation in the septal organ of Masera and fusion of the turbinates).

Table 4.5.4.1 Summary of Toxicological Doses and Endpoints for Naphthalene for Use in Dietary, Non-Occupational and Occupational Human Health Risk Assessments.				
Exposure/ Scenario	**POD**	**Uncertainty Factors**	**RfD, PAD, LOC for Risk Assessment**	**Study and Toxicological Effects**
Inhalation (Intermediate-Term)	NOAEC = 1 ppm For HEC and HED calculations see Table 4.5.4.3	UF_A = 3x UF_H = 10x	LOC = 30	**13-Week (nose-only) Inhalation Rat Study** MRID 42835901**; Subchronic (nose-only) Neurotoxicity Rat Study** MRID 44856401; NOAEC = 1 ppm (***Subchronic neurotoxicity study)*** NOAEC (***13-week inhalation study***) – not identified. Minimal LOAEC = 2 ppm (***13-week inhalation stu***dy) based on increased incidence (minimal severity) of nasal lesions (degeneration, atrophy and hyperplasia of basal cells of the olfactory epithelium; rosette formation of olfactory epithelium; atrophy and loss of Bowman's glands; hypertrophy of respiratory epithelium). These effects were of minimal severity and did not occur in control animals. LOAEC = 10 ppm (S***ubchronic neurotoxicity study***) based on nasal lesions (loss of olfactory nerve fibers, loss of bowman's glands, olfactory epithelium atrophy/disorganization, olfactory epithelium erosion/necrosis, olfactory epithelium hyperplasia, olfactory epithelium inflammatory exudate in airway, olfactory epithelium rosettes, respiratory epithelium hyperplasia).

Table 4.5.4.1 Summary of Toxicological Doses and Endpoints for Naphthalene for Use in Dietary, Non-Occupational and Occupational Human Health Risk Assessments.				
Exposure/ Scenario	**POD**	**Uncertainty Factors**	**RfD, PAD, LOC for Risk Assessment**	**Study and Toxicological Effects**
Inhalation (Long-Term)	LOAEC = 10 ppm For HEC and HED calculations see Table 4.5.4.4	UF_A = 3x UF_H = 10x UF_L = 10x	Residential LOC = 300	**Chronic Toxicity and Carcinogenicity Studies in the Rat (NTP 2000; MRID 50718701)** NOAEC (NTP 2000 rat study) = not identified LOAEC (NTP 2000 rat study) = 10 ppm based on increased incidence and severity of atypical (basal cell) hyperplasia, atrophy, chronic inflammation, and hyaline degeneration of the olfactory epithelium; hyperplasia, squamous metaplasia, hyaline degeneration, and goblet cell hyperplasia of the respiratory epithelium; and glandular hyperplasia and squamous metaplasia.
Cancer (oral, dermal, inhalation)	The carcinogenic potential of naphthalene is currently undergoing review by EPA National Center for Environmental Assessment (NCEA; Integrated Risk Information System (IRIS).			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. NOAEC = no observed adverse effect concentration. LOAEC = lowest observed adverse effect concentration. UF = uncertainty factor. UF_A = extrapolation from animal to human (intraspecies). UF_H = potential variation in sensitivity among members of the human population (interspecies). UF_L = extrapolation from LOAEL to NOAEL. UF_s = extrapolation from subchronic to chronic. LOC = level of concern. HEC = human equivalent concentration. HED = human equivalent dose.

Table 4.5.4.2. Residential Handler Calculated Inhalation (Short-term) Human Equivalent Concentrations and Doses for Naphthalene.						
Population	**Scenario**	**Toxicity duration adjustment**		**HEC[1]**		**HED[2] (mg/kg/day)**
		Daily	**Weekly**	**mg/L**	**mg/m3**	
Adult	Residential Handler	1	1	0.003	3.113	0.07

[1] HEC = human equivalent concentration.
[2] HED = human equivalent dose.
HEC = rat POD × daily duration adjustment (6 hr/6 hr for adults) × weekly daily duration adjustment (5 days/5 days) × RGDR (Regional Gas Dose Ratio)
Per the 2012 Standard Operating Procedures for Residential Exposure Assessment for daily adult handler inhalation exposures from vapors emissions.
RGDR = 0.183
HED = HEC × human-specific conversion factor (CF) × daily duration
CF = 13.8 L/min * 60 min/hr ÷ 70 kg

Table 4.5.4.3. Residential Post-Application Calculated Inhalation (Short-term) Human Equivalent Concentrations and Doses for Naphthalene.

Population	Scenario	Toxicity duration adjustment		HEC[1]		HED[2] (mg/kg/day)
		Daily	Weekly	mg/L	mg/m3	
Adult	Indoor Post-application	0.375	0.71	0.0008	0.834	0.16
Children 1 to <2 Years Old		0.333	0.71	0.0007	0.741	0.16

[1] HEC = human equivalent concentration.
[2] HED = human equivalent dose.
HEC = rat POD × daily duration adjustment (6 hr/16 hr for adults; 6/18 for children) × weekly daily duration adjustment (5 days/7 days) × RGDR (Regional Gas Dose Ratio)
Per the 2012 Standard Operating Procedures for Residential Exposure Assessment for daily adult post-application inhalation exposures from vapors emissions.
Per the 2012 Standard Operating Procedures for Residential Exposure Assessment for daily children 1 to <2 years old post-application inhalation exposures from vapors emissions.
RGDR = 0.183
HED = HEC × human-specific conversion factor (CF) × daily duration
CF = 13.8 L/min * 60 min/hr ÷ 70 kg

Table 4.5.4.4. Residential Post-Application Calculated Inhalation (Intermediate-term) Human Equivalent Concentrations and Doses for Naphthalene.

Population	Scenario	Toxicity duration adjustment		HEC[1]		HED[2] (mg/kg/day)
		Daily	Weekly	mg/L	mg/m3	
Adult	Indoor Post-application	0.375	0.71	0.000245	0.245	0.05
Children 1 to <2 Years Old		0.333	0.71	0.000218	0.218	0.05

[1] HEC = human equivalent concentration.
[2] HED = human equivalent dose.
HEC = rat POD × daily duration adjustment (6 hr/16 hr for adults; 6/18 for children) × weekly daily duration adjustment (5 days/7 days) × RGDR (Regional Gas Dose Ratio)
Per the 2012 Standard Operating Procedures for Residential Exposure Assessment for daily adult post-application inhalation exposures from vapors emissions.
Per the 2012 Standard Operating Procedures for Residential Exposure Assessment for daily children 1 to <2 years old post-application inhalation exposures from vapors emissions.
RGDR = 0.183
HED = HEC × human-specific conversion factor (CF) × daily duration
CF = 13.8 L/min * 60 min/hr ÷ 70 kg

Table 4.5.4.5. Residential Post-Application Calculated Inhalation (Long-term) Human Equivalent Concentrations and Doses for Naphthalene

Population	Scenario	Toxicity duration adjustment		HEC[1]		HED[2] (mg/kg/day)
		Daily	Weekly	mg/L	mg/m3	
Adult	Indoor Post-application	0.375	0.71	0.0029	2.899	0.55
Children 1 to <2 Years Old		0.333	0.71	0.0026	2.577	0.55

[1] HEC = human equivalent concentration.
[2] HED = human equivalent dose.
Daily duration for the rat = 6 hrs; Daily exposure for humans (16 hrs for adults; 18 hrs for children)
Animal weekly exposure = 5 days/week; human weekly exposure = 7 days/week
HEC = rat POD × daily duration adjustment (6 hr/16 hr for adults; 6/18 hr for children) × weekly daily duration adjustment (5 days/7 days) × RGDR (Regional Gas Dose Ratio)

Per the 2012 Standard Operating Procedures for Residential Exposure Assessment for daily adult post-application inhalation exposures from vapors emissions.
Per the 2012 Standard Operating Procedures for Residential Exposure Assessment for daily children 1 to <2 yrs old post-application inhalation exposures from vapors emissions.
RGDR = 0.208
HED = HEC × human-specific conversion factor (CF) × daily duration
CF = 13.8 L/min * 60 min/hr ÷ 70 kg

Table 4.5.4.6. Occupational Handler Calculated Inhalation (Short-term) Human Equivalent Concentrations and Doses for Naphthalene.

Population	Scenario	Toxicity duration adjustment		HEC[1]		HED[2] (mg/kg/day)
		Daily	Weekly	mg/L	mg/m3	
Adult	Occupational Handler	0.75	1	0.002	2.335	0.22

[1] HEC = human equivalent concentration.
[2] HED = human equivalent dose.
HEC = rat POD × daily duration adjustment (6 hr/6 hr for adults) × weekly daily duration adjustment (5 days/5 days) × RGDR (Regional Gas Dose Ratio)
Per the 2012 Standard Operating Procedures for Residential Exposure Assessment for daily adult handler inhalation exposures from vapors emissions.
RGDR = 0.183
HED = HEC × human-specific conversion factor (CF) × daily duration
CF = 13.8 L/min * 60 min/hr ÷ 70 kg

Table 4.5.4.7. Occupational Handler Calculated Inhalation (Intermediate-term) Human Equivalent Concentrations and Doses for Naphthalene.

Population	Scenario	Toxicity duration adjustment		HEC[1]		HED[2] (mg/kg/day)
		Daily	Weekly	mg/L	mg/m3	
Adult	Occupational Handler	0.75	1	0.001	0.687	0.09

[1] HEC = human equivalent concentration.
[2] HED = human equivalent dose.
HEC = rat POD × daily duration adjustment (6 hr/6 hr for adults) × weekly daily duration adjustment (5 days/5 days) × RGDR (Regional Gas Dose Ratio)
Per the 2012 Standard Operating Procedures for Residential Exposure Assessment for daily adult handler inhalation exposures from vapors emissions.
RGDR = 0.183
HED = HEC × human-specific conversion factor (CF) × daily duration
CF = 13.8 L/min * 60 min/hr ÷ 70 kg

4.6 Endocrine Disruption

As required by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA), EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its most recent registration decision for naphthalene, EPA reviewed these data and selected the most sensitive endpoints for relevant

risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), naphthalene is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[111] and includes some pesticides scheduled for registration review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[12]

5.0 Dietary Exposure and Risk Assessment

Naphthalene is a moth and animal repellant. It is a non-food use chemical, so there are no food or feed uses that require the establishment of tolerances. There is potential for drinking water exposure through run-off from the outdoor uses of naphthalene.

5.1 Residues of Concern Summary and Rationale

There are no uses for naphthalene which require residues of concern to be established for tolerance enforcement and risk assessment on food/feed crops and/or livestock. Dietary exposure may occur through drinking water and exposure estimates are for parent only (D351119, M. Corbin, 04/09/2008).

[11] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.
[12] http://www.epa.gov/endo/

5.2 Food Residue Profile

Naphthalene is an animal and moth repellent registered for application as a non-food use chemical. It is not applied to food or in ways where food contamination can occur. Thus, the registered use of naphthalene does not require the establishment of tolerances and no supporting residue chemistry data are required.

5.3 Water Residue Profile

Drinking water exposure is considered since naphthalene is used outdoors as an animal repellant. The estimated drinking water concentrations used for dietary risk assessment were provided by EFED in the "Revised Drinking Water Exposure Assessment for the Human Health Risk Assessment for the RED of Naphthalene Incorporating the Registrant's Error Correction Comments" (M. Corbin, D351119, 04/09/2008). This assessment was conducted for the 2008 RED of naphthalene and was verified to be current for use in this dietary exposure and risk assessment (electronic communication with D. Spatz, 06/18/2018). The resulting residues estimated for drinking water from this assessment were incorporated into the DEEM-FCID model as the food categories "water, direct, all sources" and "water, indirect, all sources."

The EFED assessment calculated peak (acute) and annual average (chronic) Estimated Environmental Concentrations (EECs) for naphthalene in both surface water and in ground water. These values represent the highest use rate of naphthalene as an outdoor animal repellant which has been established for treating ornamentals. Using the screening model FIRST (FQPA Index Reservoir Screening Tool), peak and annual average surface water EECs of 43.4 ppb and 6.5 ppb were calculated, respectively. In ground water, the screening model SCI-GROW (Screening Concentration in Ground Water) calculated EECs ranging from 4.5 to 0.2 ppb. Because the EECs for ground water residues are lower than those for surface water, the FIRST surface water exposure estimates are used for the drinking water risk assessment and are concluded to be protective (Table 5.3.1).

Table 5.3.1. Results of FIRST Modeling for Naphthalene.

Use Site	Application Rate (lbs/acre)	Number of Applications (interval)	Peak EEC (ppb)	Annual Average EEC (ppb)
Ornamentals for rabbit & dog repellent	10.8	6 (2 months)	**43.4**[1]	**6.5**[2]

[1.] Value used for acute dietary exposure and risk assessment.
[2.] Value used for chronic dietary exposure and risk assessment

5.4 Dietary Risk Assessment

5.4.1 Description of Residue Data Used in Dietary Assessment

Residue data are not relevant because a food dietary assessment is not required for naphthalene.

5.4.2 Percent Crop Treated Used in Dietary Assessment

Percent crop treated information is not relevant because a food dietary assessment is not required

for naphthalene.

5.4.3 Acute Dietary Risk Assessment

The acute dietary exposure analysis and risk assessment is a high-end screening level assessment of naphthalene exposure from drinking water. It is based on modeling data provided by the EFED which estimates the concentration of naphthalene in water. It was conducted for the general U.S. population and its population subgroups since an acute dietary toxicological endpoint was identified for risk assessment. The acute risk estimate for naphthalene was found to be <1% of the aRfD at the 95th percentile for the general U.S. population. The most highly exposed population subgroup was all infants < 1 year old which had an acute exposure of 1.8% of the aRfD at the 95th percentile.

5.4.4 Chronic Dietary Risk Assessment

The chronic dietary exposure analysis and risk assessment is also a high-end screening level assessment of naphthalene exposure from drinking water based on modeling data provided by EFED. It was conducted for the general U.S. population and all its population subgroups since a chronic dietary toxicological endpoint was identified for risk assessment. The chronic dietary risk estimates for naphthalene were found to be <1% of the chronic reference dose (cRfD) for the general U.S. population and all its population subgroups.

5.4.5 Summary Table

As stated above, for acute and chronic assessments, HED is concerned when the dietary risk estimate exceeds 100% of the RfD. Acute and chronic analyses were performed for naphthalene using DEEM-FCID (ver. 3.16) estimating the dietary (drinking water only) exposure of the U.S. population and various population subgroups. The results are summarized in Table 5.4.5.1. The resulting acute drinking water exposure estimates were less than HED's level of concern (<100% aRfD) for the general U.S. population and all population sub-groups at the 95th percentile of exposure. The resulting chronic drinking water exposure estimates were less than HED's level of concern (<100% cRfD) for the general U.S. population and all population subgroups.

Table 5.4.5.1 Summary of Dietary (Drinking Water) Exposure and Risk for the Naphthalene.

Population Subgroup	Acute Dietary[1] (95th Percentile)		Chronic Dietary[2]	
	Dietary Exposure (mg/kg/day)	% aRfD	Dietary Exposure (mg/kg/day)	% cRfD
General U.S. Population	0.002366	<1	0.000136	<1
All Infants (< 1 year old)	**0.007412**	**1.8**	**0.000351**	**<1**
Children 1-2 years old	0.003649	<1	0.000196	<1
Children 3-5 years old	0.002961	<1	0.000165	<1
Children 6-12 years old	0.002262	<1	0.000119	<1
Youth 13-19 years old	0.001971	<1	0.000099	<1
Adults 20-49 years old	0.002329	<1	0.000136	<1
Adults 50-99 years old	0.002074	<1	0.000134	<1
Females 13-49 years old	0.002362	<1	0.000135	<1

[1] Acute dietary analysis derived from a 0.4 mg/kg/day aRfD for the general population.
[2] Chronic dietary analysis derived from a 0.1 mg/kg/day cRfD for the general population.

[3] Highest exposures found for each assessment are noted in bold.

6.0 Residential Exposure/Risk

Residential handler inhalation and post-application inhalation exposures are expected with the application of naphthalene products. A chemical-specific study was used to assess potential inhalation exposures/risks (see Section 6.2).

6.1 Residential Handler Exposure/Risk

HED uses the term "handlers" to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct tasks related to applications and that exposures can vary depending on the specifics of each task. Residential handlers are addressed somewhat differently by HED as homeowners are assumed to complete all elements of an application without use of any protective equipment.

Although there may be potential for dermal exposures to residential handlers while applying mothball products, an exposure assessment was not conducted since a dermal endpoint was not selected.

The quantitative exposure/risk assessment developed for residential handlers is based on the following scenarios:

- Applying dust/powder (moth flakes) to indoor settings
- Applying granules (mothball granules) via hand dispersal to indoor and outdoor settings

Residential Handler Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the residential handler risk assessments. Each assumption and factor is detailed below.

Application Rate: See Table 3.3. for application rates.

Unit Exposures and Volume/Area Treated:

Due to the lack of exposure data for the application of naphthalene flakes via hand dispersal, inhalation unit exposure values for applying powders/dusts via plunger duster were used as a surrogate for the application of naphthalene flakes to indoor environments. The use of surrogate plunger duster data for flakes is considered highly conservative as it is representative of powdery type dusts, risks for moth flakes would likely be lower. Inhalation unit exposure for granule hand dispersal were used as a surrogate to represent the application of naphthalene granules to indoor and outdoor areas. Area treated assumptions are based on HED's 2012 Residential SOPs (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide) for the outdoor granules hand dispersal scenario. All other assumptions for volume treated are derived from EPA Reg No. 1475-74 to represent volumes of typical/common storage containers and closets. 12 ft^3 represents the average size of a garment bag, 18 ft^3 represents the size of a jumbo garment bag, 24 ft^3 represents the size of a large trunk, 64 ft^3 represents the size of a reach-in closet, and 200 ft^3 represents the size of a walk-in closet. The volume treated assumption of 186 ft^3 (size of closet) is derived from the chemical-specific air concentration study for naphthalene (D401780, W. Britton, 09/25/2013; MRID 43716501).

Exposure Duration:
Residential handler exposure is expected to be short-term in duration. Intermediate-term exposures are not likely because of the intermittent nature of applications by homeowners.

Residential Handler Non-Cancer Exposure and Risk Estimate Equations
The algorithms used to estimate exposure and dose for residential handlers can be found in the 2012 Residential SOPs[13].

Summary of Residential Handler Non-Cancer Exposure and Risk Estimates
Inhalation risk estimates of concern were identified for residential handlers (MOE < LOC; LOC = 30). MOEs ranged from 0.82 to 14 for the indoor application of naphthalene flakes. No risks of concern were identified for residential handlers applying granules to outdoor environments; MOE = 49. MOEs for residential handlers applying granules indoors via hand dispersal ranged from 29 to 490 (LOC = 30). A summary of these residential handler inhalation exposure and risk estimates for naphthalene are presented in Table 6.1.1

Table 6.1.1. Residential Handler Non-cancer Exposure and Risk Estimates for Naphthalene.

Exposure Scenario	Level of Concern	Inhalation Unit Exposure (mg/lb ai)	Maximum Application Rate[1]	Volume/Area Treated[2]	Inhalation	
					Dose (mg/kg/day)[3]	MOE[4] LOC = 30
Mixer/Loader/Applicator						
Moth flakes - Indoors (dust/powder plunger duster)	30	1.7	0.02 lb ai/ft^3	12 ft^3	0.0051	**14**
				18 ft^3	0.0077	**9.2**
				24 ft^3	0.01	**6.9**
				64 ft^3	0.027	**2.6**
				186 ft^3	0.079	**0.89**
				200 ft^3	0.085	**0.82**
Granules – Outdoors (granule, hand dispersal)		0.38	0.00025 lb ai/ft^2	1200 ft^2	0.0014	49
Granules – Indoors (granule, hand dispersal)		0.38	0.0025 lb ai/ft^3	12 ft^3	0.00014	490
				18 ft^3	0.00021	330
				24 ft^3	0.00029	250
				64 ft^3	0.00076	92
				186 ft^3	0.0022	32
				200 ft^3	0.0024	**29**

1 Based on registered labels in Table 3.3. All rates expressed as lb ai/ft^3, except where application rate is expressed in lb ai/ft^2.
2 Based on HED's 2012 Residential SOPs (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide) for the outdoor granules hand dispersal scenario. All other assumptions for volume treated are derived from EPA Reg No. 1475-74 to represent volumes of typical/common storage containers and closets or from the chemical specific air concentration study for naphthalene (MRID 43716501).
3 Inhalation Dose = Inhalation Unit Exposure (mg/lb ai) × Application Rate (lb ai/ft^2 or ft^3) × Volume/Area Treated (ft^2 or ft^3/day) ÷ BW (80 kg).
4 Inhalation MOE = Inhalation HED (0.07 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

[13] Available: http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

6.2 Residential Post-Application Exposure/Risk

There is the potential for post-application exposure for individuals exposed as a result of being in an environment that has been previously treated with naphthalene. The quantitative exposure/risk assessments for residential post-application exposures include:

- Inhalation exposure from mothball applications (adults and children)
- Episodic ingestion of moth flakes (children)

While there may be potential for residential post-application dermal exposure, a residential post-application dermal assessment was not conducted since a dermal endpoint was not selected for naphthalene. Exposures resulting from non-occupational spray drift or off-field bystander volatilization are not expected based on the formulation of naphthalene and how it is applied.

Incidental oral (hand to mouth) exposures are not expected. Incidental oral scenarios describe a child contacting a surface with residue from a treatment. In the case of naphthalene, the most applicable non-dietary oral exposure is episodic naphthalene flake ingestion. There is no spray or residues for a child to contact.

Episodic Ingestion

There is a possibility for the ingestion of naphthalene flakes since they are labeled for application indoors in areas potentially accessible to children (e.g., closets). Ingestion of naphthalene flakes is considered an episodic event and not a routine behavior. Because HED does not believe that this would occur on a regular basis, our concern for human health is related to acute poisoning rather than short-term residue exposure. Therefore, an acute dietary dose is used to estimate exposure and risk resulting from episodic ingestion of naphthalene flakes. For these same reasons, the episodic ingestion scenario is not recommended for inclusion in the short-term aggregate assessment.

The lifestages selected for each post-application scenario are based on an analysis provided as an Appendix in the 2012 Residential SOPs[14]. While not the only lifestage potentially exposed for these post-application scenarios, the lifestage that is included in the quantitative assessment is health protective for the exposures and risk estimates for any other potentially exposed lifestage.

Residential Post-application Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the residential post-application risk assessment. Chemical-specific air concentrations were incorporated into the post-application assessment (MRID 43716501). Each additional assumption and factor is detailed in the 2012 Residential SOPs[14].

Average 8-hour concentrations taken over 182 days were used to represent short-, intermediate-, and long-term exposure scenarios. Using an average over shorter time durations would result in similar air concentrations as the average 8-hour concentrations over 182 days.

[14] Available: http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

Application Rate
Application rates are based on labels as shown in Table 3.3.

Exposure Duration
The exposure durations for residential post-application exposures are short-, intermediate- and long-term.

Residential Post-application Exposure and Risk Equations
The algorithms used to estimate residential post-application exposure and dose can be found in the 2012 Residential SOPs[15].

Air Concentration Data
Chemical-specific air concentration data are available for naphthalene from a study of mothball use in residences (MRID 43716501) (D401780, W. Britton, 09/25/13). The study was conducted in two uninhabited residences in Georgia (one control and one treated). In the bedroom of the treated house, the test product was placed inside an open container in a closet and in an empty dresser drawer. The product was applied at the maximum label rate of 1 oz/3 ft^3 (0.063 lb ai/ft^3), therefore, 62.24 oz (3.89 lb ai/ft^3) was applied to the closet (closet size of 186.724 ft^3) and 0.41 oz (0.021 lb ai/ft^3) was applied to the dresser drawer (drawer size of 1.24 ft^3). Air monitoring was performed in both the untreated and treated residence. Seven 15-minute samples were collected at the following intervals: 1 hr prior to application and at 1, 4, 8, 12, 16, and 24 hours after application. Thirty-seven 8-hour samples were collected at the following intervals: daily between Day 2 and Day 14 after application and once weekly thereafter over the 182-day study period. One sampling location was used in the untreated house (on the bed) and three sampling locations were used in the treated house (Zone 1 - outside the closet; Zone 2 - on the dresser; and Zone 3 - on the bed).

The data used in this assessment include: (1) the average of individual measurements collected outside the closet (0.0360 mg/m^3), (2) the average of individual measurements collected on the dresser (0.0386 mg/m^3), and (3) the average of individual measurements collected on the bed (0.0362 mg/m^3) all representing 8-hour exposure durations 2 to 14 days after application and once weekly over 182 days. The maximum 15-minute samples collected from 1 to 24 hours after application were below the level of quantification (LOQ), and, therefore, were not used in this assessment. See Table 6.2.1 for a summary of the air concentration values.

Table 6.2.1. Summary of Naphthalene Indoor Air Concentrations (mg/m^3) from the Treated Residence. [a, b]

Location	n	Minimum	Maximum	Average[c]	Standard Deviation
15-min Exposure Duration Samples (1 to 24 hours after application)					
Zone 1: Outside of the closet	6	ND (0.011)	<LOQ (0.25)	(<LOQ of 0.25) 0.2101	0.0976
Zone 2: On the dresser	6	ND (0.011)	<LOQ (0.25)	(<LOQ of 0.25) 0.2101	0.0976
Zone 3: On the bed	6	<LOQ (0.25)	<LOQ (0.25)	(<LOQ of 0.25) 0.2500	0.0000
Overall	18	ND (0.011)	<LOQ (0.25)	(<LOQ of 0.25) 0.2234	0.0773

[15] http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

8-hr Exposure Duration Samples (2 to 182 days after application)					
Zone 1: Outside of the closet	37	ND (0.0011)	0.0471	0.0360	0.0085
Zone 2: On the dresser	37	<LOQ (0.0078)	0.0574	0.0386	0.0086
Zone 3: On the bed	37	0.0210	0.0459	0.0362	0.0065
Overall	111	ND (0.0011)	0.0574	0.0369	0.0079

a. ND = not detected at the LOD of 0.00215 mg/m^3 for 8-hr samples and 0.0217 mg/m^3 for the 15-minute samples. LOQ = 0.0156 mg/m^3 for 8-hr samples and 0.50 mg/m^3 for the 15-minute samples. For calculation purposes, ½ LOD was used for residues reported as ND and ½ LOQ was used for residues reported between the LOD and LOQ.
b. Air concentrations were corrected by the reviewer for the average low-level field fortification recovery of 90%.
c. Average air concentration values were not weighted

A typical episodic ingestion represents the ingestion of pesticide pellets and granules that have been applied to lawns and gardens. The scenario assumes that dry pesticide materials (pellets and granules) are ingested by children who play in treated areas (e.g., lawns, playgrounds). The typical episodic ingestion scenario is not an accurate representation of the application of moth flakes to closets. Naphthalene mothball and granule products were not considered in the episodic ingestion scenario because all mothball products are required to have the mothballs packaged in sachets[16], and the granules are required per the product labels to be applied in cheese cloths or hosiery and hung, to repel squirrels and bats in attics and wall voids. Naphthalene granules for outdoor use were not considered in the episodic ingestion scenario as children are unlikely to access outdoor areas (i.e. wood piles, trash cans, flower beds, etc.). Therefore, a screening level calculation was conducted for the episodic ingestion of moth flakes. Using the POD of 400 mg/kg/day with an uncertainty factor of 1000, for a 15 kg child, a dose of 0.006 grams or 0.00021 oz of naphthalene is needed to get an MOE of 1000. Therefore, if a child consumed more than 0.006 g or 0.00021 oz moth flakes, there would be risk estimates of concern.

Summary of Residential Post-application Exposure and Risk Estimates

All short-, intermediate-, and long-term residential post-application scenarios result in MOEs less than the LOC (short- and intermediate- term inhalation LOC=30; long-term inhalation LOC = 300) and are of concern. Short-term MOES range from 22 to 23 for adults and 19 to 21 for children (1 to < 2 years old). Intermediate-term inhalation MOEs range from 6.3 to 6.8 for adults and 5.6 to 6.1 for children (1 to < 2 years old). Long-term MOEs range from 75 to 81 for adults and 67 to 72 for children (1 to < 2 years old). A summary of the residential post-application exposure and risk estimates for naphthalene is presented in Tables 6.2.2, 6.2.3, and 6.2.4.

Table 6.2.2. Short-term Residential Post-application Exposure and Risk Estimates for Naphthalene.

Lifestage	Post-application Exposure Scenario		HEC	Average 8-hour Air Concentration	MOEs[1] (LOC = 30)
Adults	Mothball	Inhalation- Outside of the Closet	0.834 mg/m^3	0.0360 mg/m^3	23
		Inhalation – On the Dresser	0.834 mg/m^3	0.0386 mg/m^3	22
		Inhalation – On the Bed	0.834 mg/m^3	0.0362 mg/m^3	23
		Overall for all Sites	0.834 mg/m^3	0.0369 mg/m^3	23
Children		Inhalation- Outside of the Closet	0.741 mg/m^3	0.0360 mg/m^3	21

[16] There is one currently-registered naphthalene mothball product (EPA Reg. No. 91974-2) that has loose mothballs, not contained in sachets. Sachets were required for all mothball products by the naphthalene 2008 Reregistration Eligibility Decision. This product is in the process of being voluntarily cancelled by the registrant. The Federal Register Notice (FRN) announcing receipt of the request to cancel this product was published on July 10, 2018. A FRN announcing the final cancellation order is expected to publish in 2019.

Table 6.2.2. Short-term Residential Post-application Exposure and Risk Estimates for Naphthalene.					
Lifestage	Post-application Exposure Scenario		HEC	Average 8-hour Air Concentration	MOEs[1] (LOC = 30)
		Inhalation – On the Dresser	0.741 mg/m^3	0.0386 mg/m^3	19
		Inhalation – On the Bed	0.741 mg/m^3	0.0362 mg/m^3	20
		Overall for all Sites	0.741 mg/m^3	0.0369 mg/m^3	20

[1] (HEC)/(Air Concentration) = MOE

Table 6.2.3. Intermediate-term Residential Post-application Exposure and Risk Estimates for Naphthalene.					
Lifestage	Post-application Exposure Scenario		HEC	Average 8-hour Air Concentration	MOEs[1] (LOC = 30)
Adults	Mothball	Inhalation- Outside of the Closet	0.245 mg/m^3	0.0360 mg/m^3	6.8
		Inhalation – On the Dresser	0.245 mg/m^3	0.0386 mg/m^3	6.3
		Inhalation – On the Bed	0.245 mg/m^3	0.0362 mg/m^3	6.8
		Overall for all Sites	0.245 mg/m^3	0.0369 mg/m^3	6.6
Children		Inhalation- Outside of the Closet	0.218 mg/m^3	0.0360 mg/m^3	6.1
		Inhalation – On the Dresser	0.218 mg/m^3	0.0386 mg/m^3	5.6
		Inhalation – On the Bed	0.218 mg/m^3	0.0362 mg/m^3	6.0
		Overall for all Sites	0.218 mg/m^3	0.0369 mg/m^3	5.9

[1] (HEC)/(Air Concentration) = MOE

Table 6.2.4. Long-term Residential Post-application Exposure and Risk Estimates for Naphthalene.					
Lifestage	Post-application Exposure Scenario		HEC	Average 8-hour Air Concentration	MOEs[2] (LOC = 300)
Adults	Mothball	Inhalation- Outside of the Closet	2.899 mg/m^3	0.0360 mg/m^3	81
		Inhalation – On the Dresser	2.899 mg/m^3	0.0386 mg/m^3	75
		Inhalation – On the Bed	2.899 mg/m^3	0.0362 mg/m^3	80
		Overall for all Sites	2.899 mg/m^3	0.0369 mg/m^3	79
Children		Inhalation- Outside of the Closet	2.577 mg/m^3	0.0360 mg/m^3	72
		Inhalation – On the Dresser	2.577 mg/m^3	0.0386 mg/m^3	67
		Inhalation – On the Bed	2.577 mg/m^3	0.0362 mg/m^3	71
		Overall for all Sites	2.577 mg/m^3	0.0369 mg/m^3	70

[1] (HEC)/(Air Concentration) = MOE

7.0 Non-occupational Bystander Post-application Inhalation Exposure and Risk Estimates

Naphthalene is registered for indoor and outdoor uses in residential settings, and a residential post-application inhalation assessment was completed for the indoor uses as shown in Section 6.2. Although naphthalene is also registered as a granule for use in outdoor settings (houses, barns, wood piles, trash cans, flower beds, etc), post-application inhalation exposure while performing activities in previously treated outdoor areas was not assessed because the expected dilution in outdoor air would lower air concentrations to insignificant levels.

8.0 Non-occupational Spray Drift Exposure and Risk Estimates

A quantitative spray drift assessment was not conducted because the registered uses of naphthalene (indoors, and outdoor granules) are not expected to result in spray drift.

9.0 Aggregate (Combined) Exposure/Risk Characterization

Food Quality Protection Act (FQPA) considerations do not apply to naphthalene for the currently registered (non-food) use patterns described in this risk assessment: no exposure to naphthalene is expected from food based on the registered use patterns. Although there are potential exposures from drinking water (oral exposure) and from residential uses (inhalation exposure), those exposures are not combined since the PODs for the oral and inhalation exposures are not based on common toxicological effects. Episodic oral exposures are not combined with dietary drinking water exposures as the episodic exposure is considered a sporadic, one-time acute exposure.

9.1 Acute Aggregate (Combined) Risk

The acute combined risk assessment includes only drinking water exposure. The acute risk estimates are not of concern to HED for the general population and all population subgroups. Refer to section 5.4.4 for a detailed discussion of the chronic dietary assessment.

9.2 Short-, Intermediate-, and Long-Term Aggregate (Combined) Risk

Short-, intermediate-, and long-term residential post-application exposures are expected based on current use patterns. A combined risk assessment of inhalation and dietary exposure was not conducted because the PODs selected for the inhalation and oral exposure routes are not based on common toxicological effects. Since there are no residential incidental oral (i.e., hand to mouth) exposures to naphthalene based on existing registered products and use patterns, combined exposure from drinking water and incidental oral exposures is not required. Since a dermal endpoint was not selected, dermal exposures were not combined.

9.3 Chronic Aggregate (Combined) Risk

The chronic combined risk assessment includes only drinking water exposure. The chronic risk estimates are not of concern to HED for the general population and all population subgroups. Refer to section 5.4.4 for a detailed discussion of the chronic dietary assessment.

10.0 Cumulative Exposure/Risk Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to naphthalene and any other substances and naphthalene does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that naphthalene has a common mechanism of toxicity with other substances. In 2016, EPA's Office of Pesticide Programs released a guidance document entitled, *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* [https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework]. This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This

framework supplements the existing guidance documents for establishing common mechanism groups (CMGs) and conducting cumulative risk assessments (CRA). During Registration Review, the agency will utilize this framework to determine if the available toxicological data for naphthalene suggests a candidate CMG may be established with other pesticides. If a CMG is established, a screening-level toxicology and exposure analysis may be conducted to provide an initial screen for multiple pesticide exposure.

11.0 Occupational Handler Exposure/Risk Estimates

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the proposed uses. The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios:

- Applying dust/powder (moth flakes) to indoor settings
- Applying granules (mothball granules) via hand dispersal to indoor and outdoor settings

Occupational Handler Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Each assumption and factor is detailed below on an individual basis.

Application Rate: See Table 3.3. for application rates.

Unit Exposures: It is the policy of HED to use the best available data to assess handler exposure. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include PHED 1.1, the Outdoor Residential Exposure Task Force (ORETF) database, or other registrant-submitted occupational exposure studies. Some of these data are proprietary (e.g., AHETF data), and subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures", are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table[17]", which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at the Agency website[18].

Volume/Area Treated:
Due to the lack of exposure data for the application of naphthalene flakes via hand dispersal; inhalation unit exposure values for applying powders/dusts via shaker were used as a surrogate

[17] Available: https://www.epa.gov/sites/production/files/2016-11/documents/handler-exposure-table-2016.pdf
[18] Available: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

for the application of moth flakes to indoor environments. The use of surrogate shaker can data for dusts is considered highly conservative. The use of surrogate plunger duster data for dusts is considered highly conservative as it is representative of powdery type dusts, risks for moth flakes would likely be lower. Inhalation unit exposure for pellet/tablet hand dispersal were used as a surrogate to represent the application of mothball granules to indoor and outdoor areas. HED lacks volume/area treated data for the application of mothball products. Based on assumptions used in the residential handler assessment and best professional judgement, it is assumed that an occupational handler would treat 10 houses a day in an 8-hour day, which is equivalent to treating ten 200 ft^3 closets (2,000 ft^3) and ten 1200 ft^2 outdoor residential areas (12,000 ft^2). The volume and area treated are considered reasonable assumptions for an occupational handler.

Exposure Duration:
HED classifies exposures from 1 to 30 days as short-term and exposures 30 days to six months as intermediate-term. Exposure duration is determined by many things, including the exposed population, the use site, the pest pressure triggering the use of the pesticide, and the cultural practices surrounding that use site. For most agricultural uses, it is reasonable to believe that occupational handlers will not apply the same chemical every day for more than a one-month time frame; however, there may be a large agribusiness and/or commercial applicators who may apply a product over a period of weeks (e.g., completing multiple applications for multiple clients within a region).

For naphthalene, based on the proposed use, short- and intermediate-term inhalation exposures are expected based on the currently registered uses of naphthalene. Short- and intermediate-term occupational inhalation exposures may result from applying the naphthalene products. Occupational handler dermal exposures were not assessed since a dermal endpoint was not selected.

Mitigation/Personal Protective Equipment: Estimates of inhalation exposure were calculated for baseline levels of personal protective equipment (PPE). Results are presented for "baseline," defined as a single layer of clothing consisting of a long-sleeved shirt, long pants, shoes plus socks, no protective gloves, and no respirator. The naphthalene product labels do not require PPE.

Occupational Handler Non-Cancer Exposure and Risk Estimate Equations
The algorithms used to estimate non-cancer exposure and dose for occupational handlers can be found in Appendix A.

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates
Short-term inhalation risk estimates of concern were identified for occupational handlers (MOE < LOC; LOC = 30). MOEs range from 0.0042 to 1.9 for indoor applications of naphthalene flakes and granules, respectively. No risks of concern were identified for the application of naphthalene granules to outdoor environments; MOE = 150 (LOC = 30). Intermediate-term inhalation risk estimates of concern were identified for occupational handlers (MOE < LOC; LOC = 30). MOEs range from 0.0017 to 0.76 for indoor applications of naphthalene flakes and granules, respectively. No risks of concern were identified for the application of napthhalene granules to outdoor environments; MOE = 61 (LOC = 30). Occupational handler dermal exposures were not assessed since a dermal endpoint was not selected. A summary of these

occupational handler inhalation exposure and risk estimates for naphthalene are presented in Table 11.1.1 and 11.1.2.

Table 11.1.1. Occupational Handler Short-term Non-Cancer Exposure and Risk Estimates for Naphthalene.

Exposure Scenario	Crop or Target	Level of Concern	Inhalation Unit Exposure (µg/lb ai)[1] Level of PPE or Engineering control	Maximum Application Rate[2]	Volume/Area Treated or Amount Handled Daily[3]	Inhalation Dose (mg/kg/day)[4]	Inhalation MOE[5] (LOC = 100)
Mixer/Loader							
Moth flakes - (Dust/powder plunger duster)	Indoors	30	17500	0.02 lb ai/ft^3	1000 ft^3	52.5	**0.0042**
Granules – (granule, hand dispersal)	Outdoors		470	0.00025 lb ai/ft^2	12,000 ft^2	0.00148	150
Granules – Indoors (granule, hand dispersal)	Indoors		470	0.02 lb ai/ft^3	1000 ft^3	0.118	**1.9**

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data); Level of mitigation: Baseline, PPE, Eng. Controls.
2 See volume/area treated section above.
3 Based on assumptions used in the residential handler assessment
4 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/ft^3 or lb ai/ft^2) × Volume/Area Treated Daily (ft^3/day or ft^2/day) ÷ BW (80 kg).
5 Inhalation MOE = Inhalation HED (0.22 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

Table 11.1.2. Occupational Handler Intermediate-term Non-Cancer Exposure and Risk Estimates for Naphthalene.

Exposure Scenario	Crop or Target	Level of Concern	Inhalation Unit Exposure (µg/lb ai)[1] Level of PPE or Engineering control	Maximum Application Rate[2]	Volume/Area Treated or Amount Handled Daily[3]	Inhalation Dose (mg/kg/day)[4]	Inhalation MOE[5] (LOC = 100)
Mixer/Loader							
Flakes -(Dust/powder plunger duster)	Indoors	30	17500	0.02 lb ai/ft^3	1000 ft^3	52.5	**0.0017**
Granules – (granule, hand dispersal)	Outdoors		470	0.00025 lb ai/ft^2	12,000 ft^2	0.00148	61
Granules – Indoors (granule, hand dispersal)	Indoors		470	0.02 lb ai/ft^3	1000 ft^3	0.118	**0.76**

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data); Level of mitigation: Baseline, PPE, Eng. Controls.
2 See volume/area treated section above.
3 Based on assumptions used in the residential handler assessment
4 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/ft^3 or lb ai/ft^2) × Volume/Area Treated Daily (ft^3/day or ft^2/day) ÷ BW (80 kg).
5 Inhalation MOE = Inhalation HED (0.09 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

11.2 Occupational Post-application Exposure/Risk Estimates

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure.

Occupational post-application exposures are not expected, as occupational handlers who apply mothball products in a residential setting would not be expected to remain in that residential setting for a time period sufficient to result in significant exposure.

12.0 Public Health and Pesticide Epidemiology Data References

Incident Report Memo: D449351, S. Recore and E. Evans, 11/15/2018

Naphthalene incidents were previously reviewed in 2016 (5/25/16, #D433256, S. Recore and E. Evans). In the 2016 review, a relatively high number of incidents were reported in two datasets, SENSOR-Pesticides and National Pesticide Information Center (NPIC), while there were few cases reported in the Incident Data System (IDS). The 2016 memo concluded that HED would provide an updated review of naphthalene incidents during registration review.

For this updated review IDS, SENSOR-Pesticides, and NPIC were reviewed. The IDS analysis from January 1, 2013 to February 14, 2018, found only three incidents involving naphthalene reported to Main IDS and 61 cases reported to Aggregate IDS. A query of SENSOR-Pesticides from 2013-2014 identified 74 cases involving naphthalene. Naphthalene incidents reported to NPIC from January 1, 2016 to February 14, 2018, 279 human incidents were reported to NPIC regarding naphthalene. [19]

This updated naphthalene incident review found that the mitigations enacted, via the 2008 RED, to prevent children from ingesting naphthalene mothball products have effectively reduced the number of child, and all, ingestion incidents reported. The number of naphthalene ingestion incidents reported to NPIC has decreased over time, down from 135 ingestion incidents reported in 2008 to only five ingestion incidents reported in 2017. However, this updated incident review also found that a fair number of naphthalene incidents continue to occur. NPIC and SENSOR-Pesticides found that homeowner use of mothballs, and subsequent inhalational exposure, led to the majority of naphthalene illness incidents. In SENSOR, 74 cases involving naphthalene were reviewed (2013-2014). One case was high in severity, ten cases were moderate in severity, and 63 cases were low in severity (all SENSOR cases must exhibit a minimum of two symptoms). The high severity case was a one-year-old child who was found chewing a mothball at home. This child developed hemolysis, vomiting, cough, and diarrhea and spent 12 days in a hospital. Health effects most frequently reported by SENSOR cases were: headache, diarrhea,

[19] The contact number on the naphthalene product labels' (see the First Aid box on labels) is for the NPIC hotline. Therefore, NPIC receives the bulk of consumer calls regarding naphthalene products.

nausea, and vomiting. In NPIC, 99 symptomatic incidents that were reviewed, 12 were classified as having moderate severity and 87 were classified as having minor severity (1/1/16 – 2/14/18). The symptoms most often reported to NPIC were neurological (n=60), respiratory (n=49), gastrointestinal (n=25), ocular (n=20), and dermal (n=7). Neurological symptoms reported include headaches, dizziness, lightheadedness, difficulty focusing, confusion, and tingling sensation. Respiratory symptoms reported included difficulty breathing, coughing, throat irritation, nose irritation, asthma attack, congestion, sneezing, and nosebleed. Gastrointestinal symptoms reported were nausea, lack of appetite, stomach pain, diarrhea, and vomiting. Ocular symptoms reported were itching eyes, irritated eyes, burning eyes, and stinging eyes. Dermal symptoms reported include rash, sores, dermal irritation, itchiness, and swelling. Many individuals were made ill after placement of mothballs all around the interior and exterior of their homes, including in closets, attics, crawlspaces, basements, under beds, on patios, and in walls. Further, many naphthalene incidents stemmed from use of mothballs to control rodents, snakes, and bats; these three pests are not registered uses on mothball labels. However, there were also several incidents that involved use of non-mothball naphthalene products which are registered as vertebrate pest repellents. Therefore, the registered vertebrate pest repellent products should be considered along with any potential future naphthalene mitigations.

13.0 References

D401780. A 180-Day Indoor Air Monitoring Study Estimating Naphthalene Levels in Air Following Residential Application of an EPA-Registered Naphthalene Mothball Product. W. Britton. 09/25/2013.

D335946. HED Chapter of the Reregistration Eligibility Decision Document (RED). D. Drew et. al. 02/22/2008.

D431829. Naphthalene Human Health Risk Assessment Scoping Document in Support of Registration Review. D. Drew. et. al. 06/27/2016.

D449351. Tier I (Scoping) Review of Human Incidents and Epidemiology. S. Recore and E. Evans. 11/15/2018.

D335944. Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision (RED). W. Britton. 02/27/2008.

D448005. Naphthalene. Acute, Chronic, and Cancer Dietary Exposure and Risk Assessments of Drinking Water to Support Registration Review. P. Savoia.

Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.500) for a non-food use for naphthalene are in Table A.1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Study		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	CR	--
870.3200	21/28-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	---
870.3465	90-Day Inhalation	no	---
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes[20]
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5395	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	CR	---
870.6100b	90-Day Neurotoxicity (hen)	no	---
870.6200a	Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b	Chronic Neurotox. Screening Battery (rat)	yes	yes
870.6300	Develop. Neuro	CR	---
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	no	---
870.7800	Immunotoxicity	yes	yes

[20] Waiver recommended by HASPOC (Nov 1, 2018 meeting; TXR# 0057813; 11/28/2018)

A.2 Toxicity Profiles

Table A.2.a Acute Toxicity of Naphthalene.

GDLN	Study Type	MRID	Results	Tox Category
870.11	Acute Oral - rat	00148174	LD_{50}: 2649 mg/kg (♂+♀)	III
870.12	Acute Dermal	00148409	LD_{50} >2000 mg/kg (♂+♀)	III
870.13	Acute Inhalation	00144557	LC_{50} > 0.4 mg/L (77.7 ppm) (♂+♀)	II
870.24	Primary Eye Irritation	00148408	Slight-moderate irritation	III
870.25	Primary Skin Irritation	00148177	Moderate irritation	III
870.26	Dermal Sensitization	00148173	Nonsensitizer – guinea pig	N/A

Table A.2.b. Subchronic, Chronic and Other Toxicity.

Guideline No./Study Type	Doses tested and Results
Nonguideline 90-Day oral toxicity – rat NTP 1980a MRID 50731301	Doses: 0, 25, 50, 100, 200, or 400 mg/kg/day (gavage; corn oil) NOAEL = 100 mg/kg/day (males/females) LOAEL = 200 mg/kg/day (males/females) based on decreased body weight gain. Renal lesions in males at 200 mg/kg (minimal cortical focal lymphocytic infiltrate; focal tubular regeneration) and 400 mg/kg (cortical diffuse tubular degeneration). At 400 mg/kg/day, clinical signs (lethargy, hunched posture) and roughened hair coat in both sexes. 2/10 females at 400 mg/kg displayed moderate lymphoid depletion of thymus.
Nonguideline 90-Day oral toxicity – B6C3F1 Mouse NTP 1980b	Doses: 0, 12.5, 25, 50, 100 or 200 mg/kg/day (gavage; corn oil) NOAEL = 100 mg/kg/day (males/females) LOAEL = 200 mg/kg/day based on transient clinical signs (rough hair and lethargy) at weeks 3 and 4.
Nonguideline 90-Day oral toxicity – CD1 Mouse Shopp et al. 1984	Doses: 5.3, 53 or 133 mg/kg/day (gavage; corn oil) NOAEL = 53 mg/kg/day mg/kg/day Possible LOAEL = 133 mg/kg/day based on >10% decreases in absolute weights of the brain, liver and spleen in females and decreased relative spleen weights in females. However, no histopathological examinations were performed. Decreased absolute and relative spleen weights also noted in females after 14-day treatment with 267 mg/kg naphthalene, but no histological examinations were performed. Mortality observed at 267 mg/kg/day. Immunotoxicity assays were negative.

Table A.2.b. Subchronic, Chronic and Other Toxicity.	
Guideline No./Study Type	**Doses tested and Results**
870.3250 90-Day dermal toxicity – rat MRID 40021801 Acceptable guideline	Doses: 0, 100, 300, or 1000 mg/kg/day (technical grade; applied as a neat solid under occlusion for 6 hrs/day, 5d/wk) NOAEL = 300 mg/kg/day (males/females) LOAEL = 1000 mg/kg/day based on atrophy of seminiferous tubules in males; non-neoplastic lesions in cervical lymph node, liver, thyroid, kidneys, urinary bladder and skin in females. Both sexes also displayed increased incidence and severity of excoriated skin and papules.
870.3700a Prenatal developmental – rat NTP 1991 (MRID 50718702)	Doses: 0, 50, 150 or 450 mg/kg/day (gavage; corn oil) **Maternal** NOAEL = 50 mg/kg/day LOAEL = 150 mg/kg/day based on persistent clinical signs of lethargy, slow breathing, rooting behavior, and significant decreases in body weights/body weight gains and food and water consumption. **Developmental** NOAEL = 450 mg/kg/day LOAEL = not identified
870.3700b Prenatal developmental – rabbit NTP 1992 (MRID 50718703)	Doses: 0, 20, 80, or 120 mg/kg/day (gavage; corn oil) **Maternal** NOAEL = 120 mg/kg/day LOAEL = not identified **Developmental** NOAEL = 120 mg/kg/day LOAEL = not identified
870.6200a Acute Neurotoxicity (Oral) Study – rat MRID 44282801 Acceptable Guideline	Doses: 0, 400, 800, or 1200 mg/kg/day (gavage; corn oil) NOAEL = not identified LOAEL = 400 mg/kg based on clinical signs (piloerection, fast respiration, hunch posture), reduced motor activity, lower body temperature, and head shaking and increased urination and defecation in the open field.
870.6200a Subchronic Neurotoxicity (inhalation) Study – rat MRID 44856401 Acceptable Guideline	Concentrations: 0, 1, 10, or 60 ppm (0, 0.005, 0.052, and 0.329 mg/L). 6hrs/day; 5 d/wk. (nose-only exposure) NOAEC = 1ppm LOAEC = 10 ppm (males/females) based on nasal lesions (loss of olfactory nerve fibers, loss of bowman's glands, olfactory epithelium atrophy/disorganization, olfactory epithelium erosion/necrosis, olfactory epithelium hyperplasia, olfactory epithelium inflammatory exudate in airway, olfactory epithelium rosettes, respiratory epithelium hyperplasia.
Nonguideline 4-Week Inhalation – rat MRID 42934901 Acceptable nonguideline	Concentrations: 0, 1, 3, 10, 30 or 77 ppm (0, 0.005, 0.016, 0.052, 0.157, or 0.404 mg/L). 6hrs/day; 5 d/wk. (nose-only exposure) NOAEL = 3 ppm LOAEL = 10 ppm (males/females) based on increased incidence and severity of nasal lesions (slight disorganization, rosette formation, basal cell hyperplasia, erosion, atrophy, and degenerate cells in the olfactory epithelium; loss of bowman's glands; respiratory epithelium hypertrophy; rosette formation in the septal organ of Masera and fusion of the turbinates).

Table A.2.b. Subchronic, Chronic and Other Toxicity.	
Guideline No./Study Type	**Doses tested and Results**
870.3465 90-day inhalation – rat MRID 42835901 Acceptable guideline	0, 2, 10 or 60 ppm (0, 0.010, 0.052 or 0.315 mg/L). 6hrs/day; 5 d/wk. (nose-only exposure) NOAEC = not identified Minimal LOAEC = 2 ppm based on increased incidence (minimal severity) of nasal lesions (degeneration, atrophy and hyperplasia of basal cells of the olfactory epithelium; rosette formation of olfactory epithelium; loss of Bowman's glands; hypertrophy of respiratory epithelium).
Nonguideline Chronic toxicity/carcinogenicity (chamber) Inhalation – rat NTP 2000 (MRID 50718701) Acceptable nonguideline	Concentrations: 0, 10, 30, or 60 ppm. 6hrs/day; 5 d/wk. (Chamber) NOAEL = not identified. LOAEL = 10 ppm, based on increased incidence and severity of atypical (basal cell) hyperplasia, atrophy, chronic inflammation, and hyaline degeneration of the olfactory epithelium; hyperplasia, squamous metaplasia, hyaline degeneration, and goblet cell hyperplasia of the respiratory epithelium; and glandular hyperplasia and squamous metaplasia.
Chronic toxicity/carcinogenicity (chamber) Inhalation – mouse NTP 1992 (MRID 42458301)	Concentrations: 0, 10, or 30 ppm. 6hrs/day; 5 d/wk. (Chamber) NOAEL = not identified. LOAEL = 10 ppm increased incidence and severity of chronic inflammation, metaplasia of the olfactory epithelium, and hyperplasia of respiratory epithelium. There was also increased incidence and severity of chronic inflammation in the lung.
870.5100 Gene mutation in *S. typhimurium* MRID 42071602 Acceptable guideline	Naphthalene (99.9%) was not mutagenic in S. typhimurium strains TA98, TA100, TA1535, TA1537 or TA1538 up to cytotoxic concentrations (300 µg/plate ± S9)
870.5265 Gene mutation in *S. typhimurium* NTP 2000	Naphthalene was negative in S. typhimurium strains TA98, TA100, TA1535, TA1537 or TA1538 up to cytotoxic concentrations (100 µg/plate ± S9) in two separate trials using the pre-incubation modification to the standard assay and S9 derived from hamster and Aroclor 1254-induced rat livers.
870.5375 CHO chromosome aberration NTP 2000	Structural aberrations (types not reported) were observed only in the presence of S9 activation, over a concentration range of 30 to 67.5 µg/mL. Based on cell cycle data from the SCE assay, the harvest time was extended to 20.5 hours to allow accumulation of a sufficient number of metaphases to score and to demonstrate a clastogenic effect in the CHO chromosome aberration assay.

Table A.2.b. Subchronic, Chronic and Other Toxicity.	
Guideline No./Study Type	**Doses tested and Results**
870.5375 CHO Sister Chromatid Exchange NTP 2000	Naphthalene induced significant and concentration-related increases in SCEs in CHO cells within a concentration range of 27 to 90 µg/mL ± S9).
870.5395 *In vivo* mouse bone marrow micronucleus MRID 42071603 Acceptable guideline	Naphthalene was negative for micronuclei induction in the bone marrow of CD-1 male and female mice up to the maximum tolerated dose (250 mg/kg) administered by intraperitoneal injection (corn oil vehicle).
870. 5550 UDS assay MRID 42071604 Acceptable guideline	Naphthalene did not induce UDS in primary rat hepatocytes up to insoluble (≥ 166 µg/mL) and cytotoxic (≥ 50 µg/mL) concentrations.

Appendix B. Physical/Chemical Characteristics

Table 3.2. Physiochemical Properties		
Parameter	Value	Reference
Molecular Weight	128.17	D322965, D. Rate, 12/20/2005
Melting point/range	80.2°C	
pH	NA	
Density	1.162	
Water solubility	Water: 31 mg / L @25°C (insoluble)	
Solvent solubility	soluble in benzene, alcohol, ether, acetone	
Vapor pressure	0.085 mm Hg @ 25°C 1 mm Hg @ 53°C	
Dissociation constant, pKa	NA/NS	
Octanol/water partition coefficient, logP_{OW} (25°C)	Log Kow = 3.30	
UV/visible absorption spectrum	ϵ_{221} = 133000 ϵ_{286} = 9300 ϵ_{312} = 289	

Appendix C. Dietary Exposure Analysis Files

Acute Dietary Input File (Drinking Water only)

Filename: E:\Naphthalene\055801 Naphthalene_Acute Input File_Reg Rev_July 30 2018_Water only.r08
Chemical: 005801 Naphthalene
RfD(Chronic): .1 mg/kg bw/day NOEL(Chronic): 0 mg/kg bw/day
RfD(Acute): .4 mg/kg bw/day NOEL(Acute): 0 mg/kg bw/day
Date created/last modified: 07-30-2018/10:43:56 Program ver. 3.16, 03-08-d
Comment: 005801 Naphthalene Registration Review July 2018 Drinking Water only

EPA Code	Crop Grp	Commodity Name	Def Res (ppm)	Adj.Factors #1	#2	Comment
8601000000	86A	Water, direct, all sources	0.043400	1.000	1.000	
8602000000	86B	Water, indirect, all sources	0.043400	1.000	1.000	

Chronic Dietary Input File (Drinking Water only)

Filename: E:\Naphthalene\055801 Naphthalene_Chronic Input File_Reg Rev_July 30 2018_Water only.r08
Chemical: 005801 Naphthalene
RfD(Chronic): .1 mg/kg bw/day NOEL(Chronic): 0 mg/kg bw/day
RfD(Acute): .4 mg/kg bw/day NOEL(Acute): 0 mg/kg bw/day
Date created/last modified: 07-30-2018/10:43:56 Program ver. 3.16, 03-08-d
Comment: 005801 Naphthalene Registration Review July 2018 Drinking Water only

EPA Code	Crop Grp	Commodity Name	Def Res (ppm)	Adj.Factors #1	#2	Comment
8601000000	86A	Water, direct, all sources	0.006500	1.000	1.000	
8602000000	86B	Water, indirect, all sources	0.006500	1.000	1.000	

Acute Dietary Results (Drinking Water only)

US EPA Ver. 3.18, 03-08-d
DEEM-FCID ACUTE Analysis for 005801 NAPHTHALENE NHANES 2003-2008 2-Day
Residue file: 055801 Naphthalene_Acute Input File_Reg Rev_July 30 2018_Water only.r08
Adjustment factor #2 NOT used.
Analysis Date: 07-30-2018/11:01:06 Residue file dated: 07-30-2018/10:43:56
RAC/FF intake summed over 24 hours
Run Comment: "005801 Naphthalene Registration Review July 2018 Drinking Water only"

Summary calculations--per capita:

	95th Percentile Exposure	% aRfD	99th Percentile Exposure	% aRfD	99.9th Percentile Exposure	% aRfD
Total US Population:						
	0.002366	0.59	0.003902	0.98	0.007413	1.85
All Infants:						
	0.007412	1.85	0.010040	2.51	0.014714	3.68
Children 1-2:						
	0.003649	0.91	0.005495	1.37	0.013532	3.38
Children 3-5:						
	0.002961	0.74	0.004535	1.13	0.007279	1.82
Children 6-12:						
	0.002262	0.57	0.003713	0.93	0.005723	1.43
Youth 13-19:						
	0.001971	0.49	0.003246	0.81	0.004901	1.23
Adults 20-49:						
	0.002329	0.58	0.003466	0.87	0.005042	1.26
Adults 50-99:						
	0.002074	0.52	0.003145	0.79	0.004958	1.24
Female 13-49:						
	0.002362	0.59	0.003473	0.87	0.004871	1.22

Chronic Dietary Results (Drinking Water only)

US EPA Ver. 3.16, 03-08-d
DEEM-FCID Chronic analysis for 005801 NAPHTHALENE NHANES 2003-2008 2-day
Residue file name: E:\Naphthalene\055801 Naphthalene_Chronic Input File_Reg Rev_July 30 2018_Water only.r08
Adjustment factor #2 NOT used.
Analysis Date 07-30-2018/11:03:01 Residue file dated: 07-30-2018/10:46:09
Reference dose (RfD, Chronic) = .1 mg/kg bw/day
COMMENT 1: 005801 Naphthalene Registration Review July 2018 Drinking Water only

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Percent of Rfd
Total US Population	0.000136	0.1%
Hispanic	0.000130	0.1%
Non-Hisp-White	0.000140	0.1%
Non-Hisp-Black	0.000112	0.1%
Non-Hisp-Other	0.000157	0.2%
Nursing Infants	0.000123	0.1%
Non-Nursing Infants	0.000453	0.5%
Female 13+ PREG	0.000128	0.1%
Children 1-6	0.000174	0.2%
Children 7-12	0.000113	0.1%
Male 13-19	0.000094	0.1%
Female 13-19/NP	0.000105	0.1%
Male 20+	0.000127	0.1%
Female 20+/NP	0.000143	0.1%
Seniors 55+	0.000132	0.1%
All Infants	0.000351	0.4%
Female 13-50	0.000135	0.1%
Children 1-2	0.000196	0.2%
Children 3-5	0.000165	0.2%
Children 6-12	0.000119	0.1%
Youth 13-19	0.000099	0.1%
Adults 20-49	0.000136	0.1%
Adults 50-99	0.000134	0.1%
Female 13-49	0.000135	0.1%

Appendix D. Search Parameters for Naphthalene Toxicology Literature Review

Date and Time of Search: 08/02/2018; 01:21 pm
Search Details:
((“*Naphthalene”*)) AND (rat OR mouse OR dog OR rabbit OR monkey OR mammal)

PubMed hits: 3401
Number of Swift Articles: 2084 for Animal
Number of Swift Articles: 2049 for Human
Number of Swift Articles: 0 for No Tag